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4*H*-Dewar Pyridines: Dearomative approach towards programmable piperidine isosteres

Tesi di Dottorato di

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ABSTRACT

Piperidine is the most frequently encountered aliphatic heterocycle in medicinal chemistry. Despite its prevalence, there is a constant demand for improvement of ADME (absorption, distribution, metabolism, excretion) properties of piperidine-containing drugs and drug candidates. 2-azabicyclo[2.2.0]hexanes present an exciting class of more rigid and structurally programmable piperidine isosteres. EVA (exit vector analysis) of the most frequently employed piperidine isosteres and 2-azabicyclo[2.2.0]hexanes is presented, and a side-by-side comparison is made. This dissertation describes our endeavors towards the expansion of accessible 2-azabicyclo[2.2.0]hex-5-ene chemical space, our exploration of 2-azabicyclo[2.2.0]hex-5-ene scaffold reactivity in olefin functionalization reactions and installation of synthetically useful handles. The malleability and practicality of 2-azabicyclo[2.2.0]hexane core is demonstrated by preparation of several isosteres of piperidine-containing drugs and lead compounds. A general blueprint for functionalized 2-azabicyclo[2.2.0]hexanes is devised. Special attention is devoted to "pseudoaxial" C5-substituted-2-azabicyclo[2.2.0]hexanes, which could serve as piperidine isosteres in their thermodynamically unfavorable axial conformations without the need to introduce additional carbon atoms.

La piperidina è l'eterociclo alifatico più frequente nella chimica farmaceutica (medicinal chemistry). Nonostante la sua prevalenza, c'è una costante domanda for il miglioramento delle proprietà ADME (assorbimento, distribuzione, metabolismo, escrezione) di farmaci e candidati farmaci contenenti strutture piperidiniche. Gli 2-azabiciclo[2.2.0]esani rappresentano un'interessante classe di isosteri della piperidina più rigidi e programmabili strutturalmente. L'EVA (exit vector analysis, analisi di vettore di uscita) degli isosteri della piperidina più frequentemente utilizzati e di 2-azabiciclo[2.2.0]esani viene mostrata, ed è stata eseguita una comparazione tra loro. Questa tesi descrive i nostri sforzi verso l'espansione di spazio chimico accessibile dei 2-azabiciclo[2.2.0]es-2-eni, la nostra esplorazione della reattività della struttura di tipo 2-azabiciclo[2.2.0]es-2-ene nelle reazioni di funzionalizzazione delle olefine e l'installazione di appigli sinteticamente utili. La malleabilità e praticabilità del nucleo di tipo 2-azabiciclo[2.2.0]es-2-ene è dimostrata dalla preparazione di diversi isosteri di farmaci e composti guida, contenenti strutture piperidiniche. Un progetto generale per la funzionalizzazione di 2-azabiciclo[2.2.0]es-2-eni è stato elaborato. Un'attenzione particolare è stata riservata ai 2-azabiciclo[2.2.0]es-2-eni con sostituenti sul C5 "psuedoassiali", che possono servire come isosteri di piperidine nella loro conformazione assiale termodinamicamente sfavorevole, senza la necessità di introdurre atomi di carbonio addizionali.

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CONTENTS

1. LIST OF ABBREVIATIONS

9BBN	9-borabicyclo(3.3.1)nonane
acac	acetylacetone
ADME	absorption, distribution, metabolism, and excretion
Alloc	allyloxycarbonyl
Ar	aryl
Boc_2O	di-*tert*-butyl dicarbonate
Cbz	benzyloxycarbonyl
COD	1,5-cyclooctadiene
CDI	carbonyldiimidazole
CYP450	cytochrome P450
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminium hydride
diglyme	bis(2-methoxyethyl) ether
DIPEA	*N,N*-diisopropylethylamine
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dpm	2,2,6,6-tetramethyl-3,5-heptanedione
DPPA	diphenylphosphoryl azide
DTBP	di-*tert*-butyl peroxide
dtbpy	4,4′-di-*tert*-butyl-2,2′-dipyridyl
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
EVA	exit vector analysis
FDA	Food and Drug Administration

FMO	flavin-containing monooxygenase
HAT	hydrogen atom transfer
HbF	fetal hemoglobin
hERG	human Ether-à-go-go-Related Gene
HOAt	1-hydroxy-7-azabenzotriazole
HWE	Horner–Wadsworth–Emmons reaction
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminum hydride
LED	light-emitting diode
MAO	monoamine oxidase
*m*CPBA	3-chloroperbenzoic acid
MHAT	metal-hydride hydrogen atom transfer
NHP	*N*-hydroxyphthalimide
NMDAR	*N*-methyl-*D*-aspartate receptor
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PARPi	poly(ADP-ribose) polymerase inhibitors
PG	protecting group
PIDA	(diacetoxyiodo)benzene
ppy	2-phenylpyridiyl
RPM	revolutions per minute
SAR	structure–activity relationship
SET	single electron transfer
SOS1	son of sevenless homologue 1
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMANO	trimethylamine *N*-oxide
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Troc	2,2,2-trichloroethoxycarbonyl
Ts	tosyl

2. INTRODUCTION

A 2014 study from Njardarson et al. highlighted the importance of nitrogen heterocycles as structural components of pharmaceuticals.[1] Out of 1086 analyzed unique small molecule drugs, 273 contained a nonaromatic six-membered nitrogen heterocycle, and 72 of those drugs contained a piperidine core. Taken together, piperidine turned out to be the most common heterocycle present in FDA-approved drugs, followed by pyridine and piperazine (Figure 1).

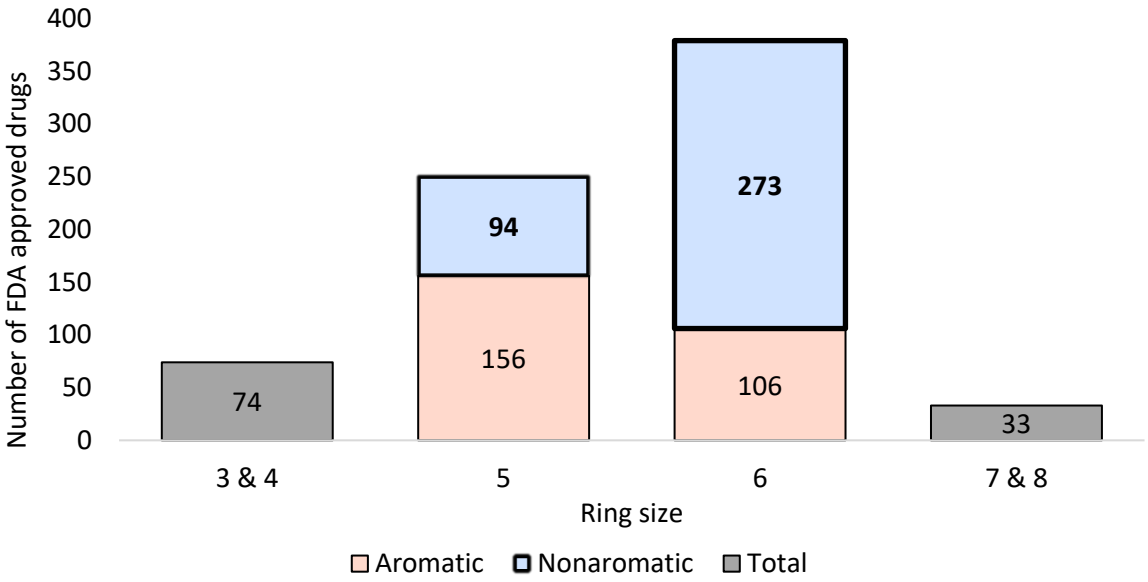


Figure 1: Nitrogen heterocycles in FDA approved drugs (until 2014).

Since 2014, 29 new small-molecule drugs or small-molecule drug mixtures containing piperidine cores have been approved by the aforementioned agency (excluding tetrahydroquinolines and tetrahydroisoquinolines and other annulated piperidine cores).[2] This equals a 40% increase in total number in less than a decade. Their structures are depicted in the following figures (Figure 2, Figure 3).

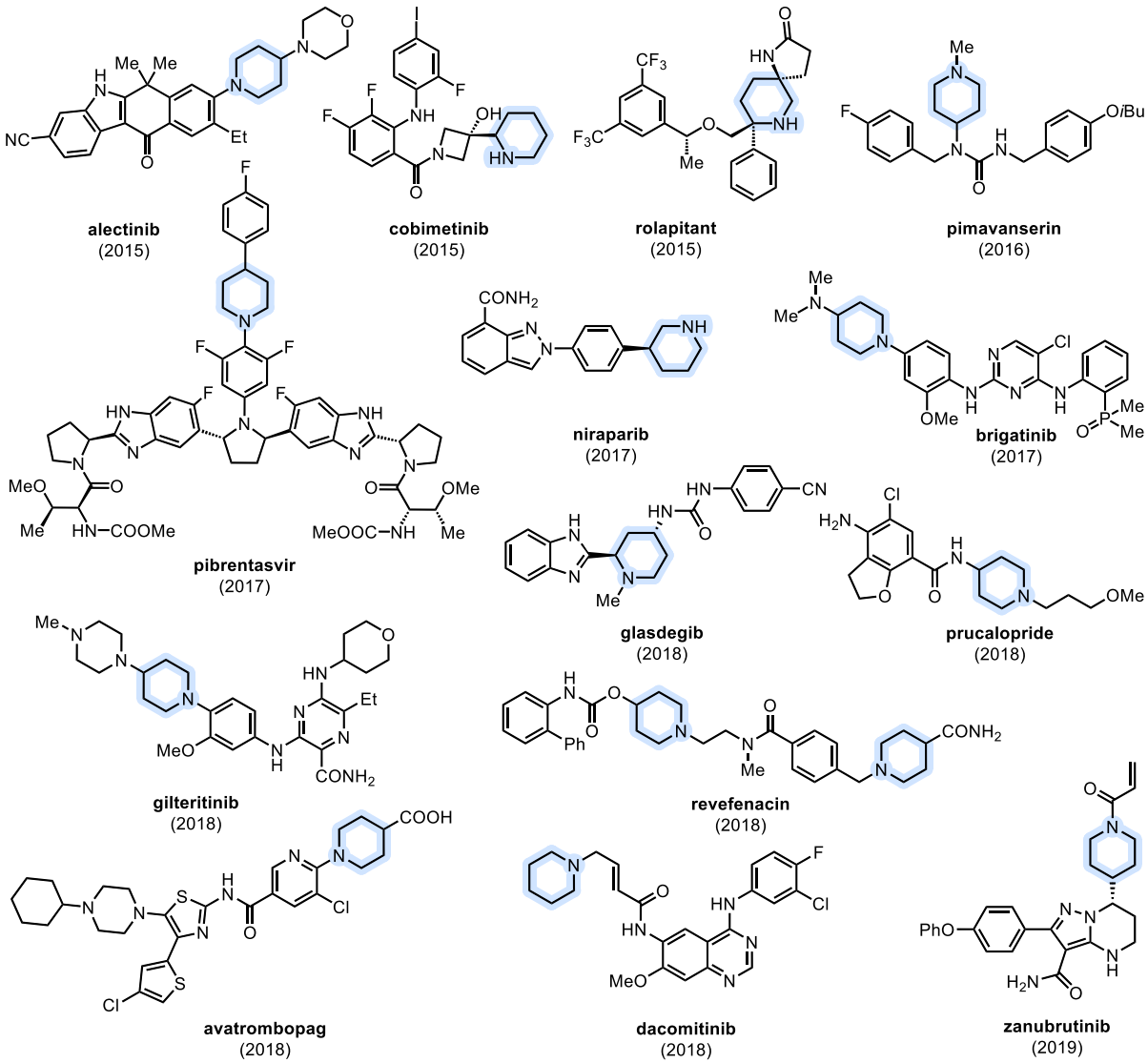


Figure 2: New FDA approved piperidine containing small molecule drugs (2015-2022).

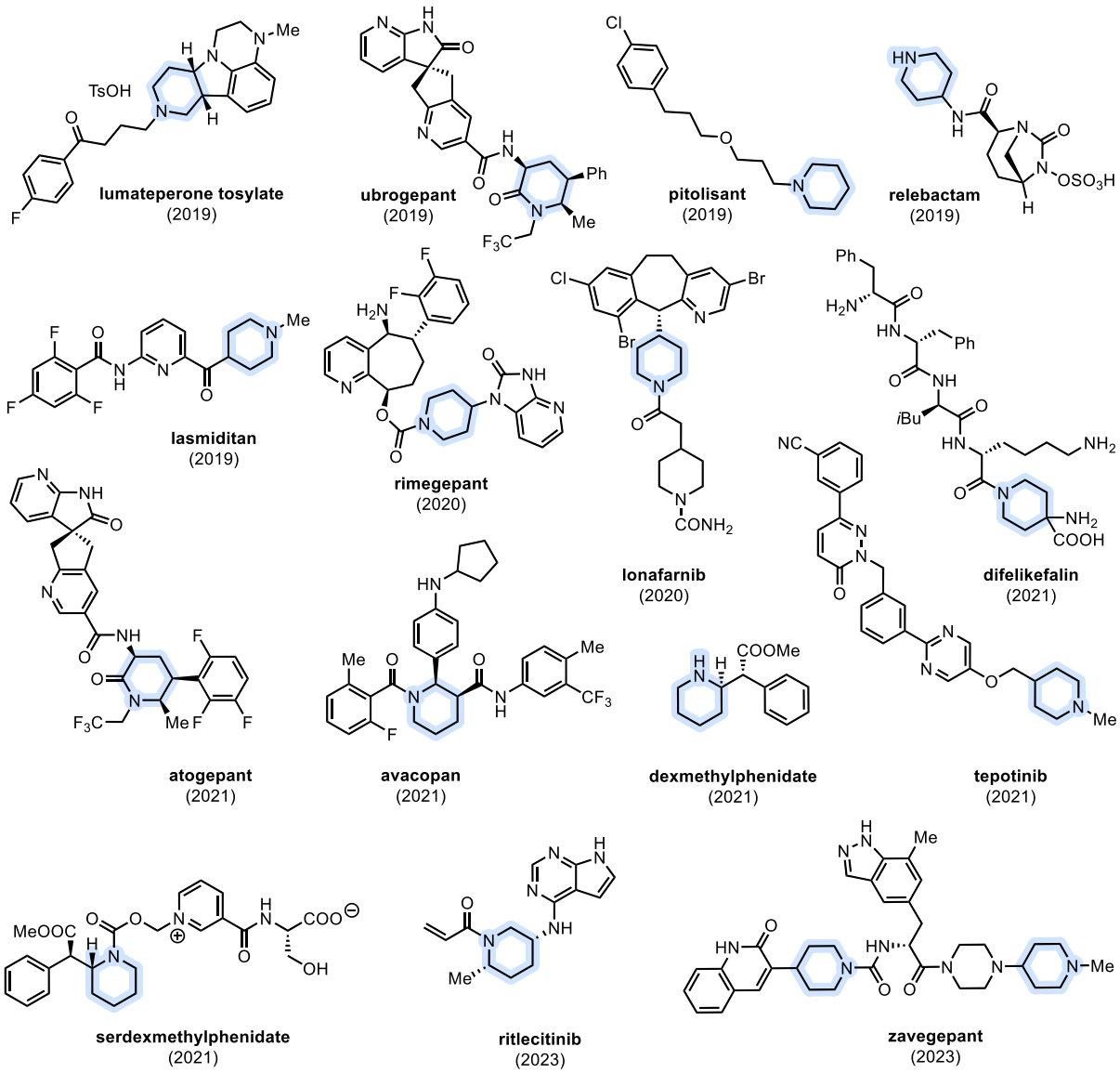


Figure 3: New FDA approved piperidine containing small molecule drugs (2015-2022), continued.

According to the 2014 analysis, 86% (62/72) of unique small molecule FDA approved piperidine containing drugs had a substituent on the nitrogen atom (N1), and 58% of them (42/72) had a

substituent at the C4 position. The majority of these drugs (61%) were disubstituted. Examples of mono-, tri- tetra-, and even penta-substituted piperidines are identified below (Figure 4).

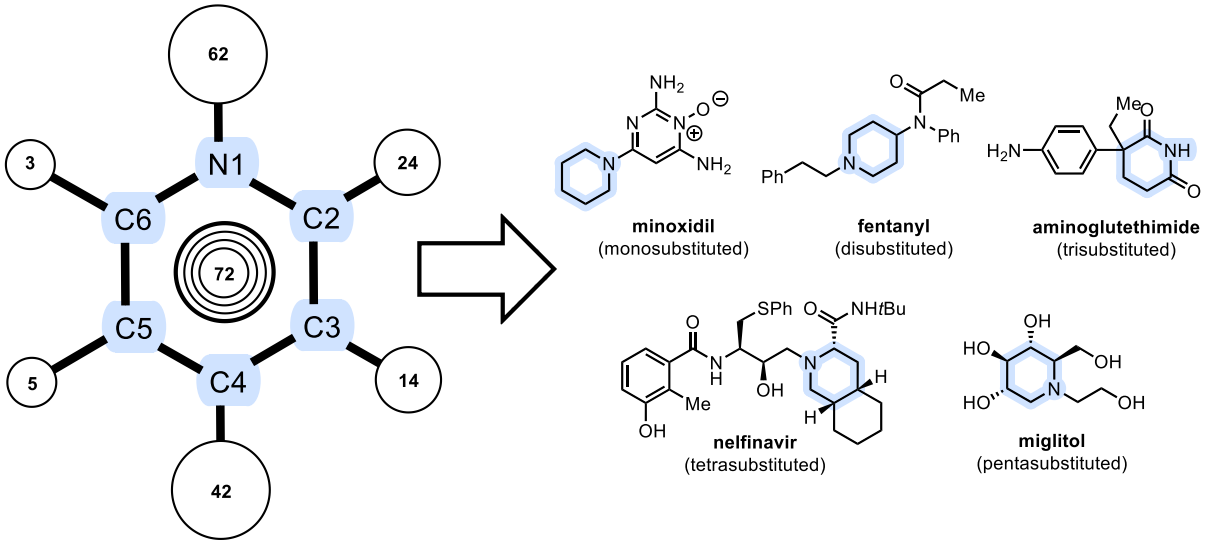
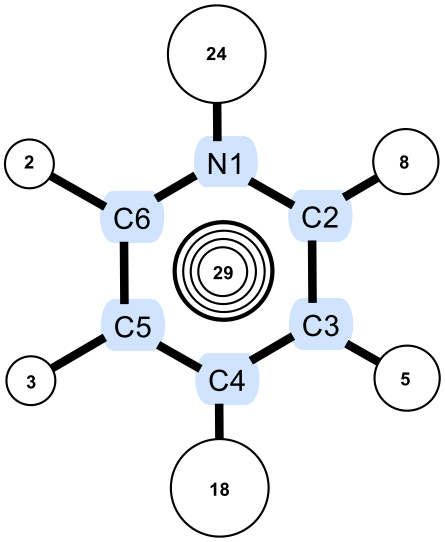


Figure 4: Substitution pattern analysis of FDA-approved piperidine containing small molecule drugs (before 2014) and relevant examples.

Out of 29 new small molecule piperidine-containing drugs, approved since 2014, 18 contain a substituent at the C4 position (62%), which is consistent with the trend from the past (

Figure 5).



Position	Before 2014	After 2014
N1	86%	83%
C2	33%	28%
C3	19%	17%
C4	58%	62%
C5	7%	10%
C6	4%	7%

Figure 5: Substitution pattern analysis of FDA-approved piperidine containing small molecule drugs (after 2014).

These findings further justify the recognition of 4-substituted (hetero)arylpiperidines as privileged fragments in drug discovery.[3] This motif is ubiquitous in drug leads across major therapeutic areas and modalities (Figure 6).[4–7]

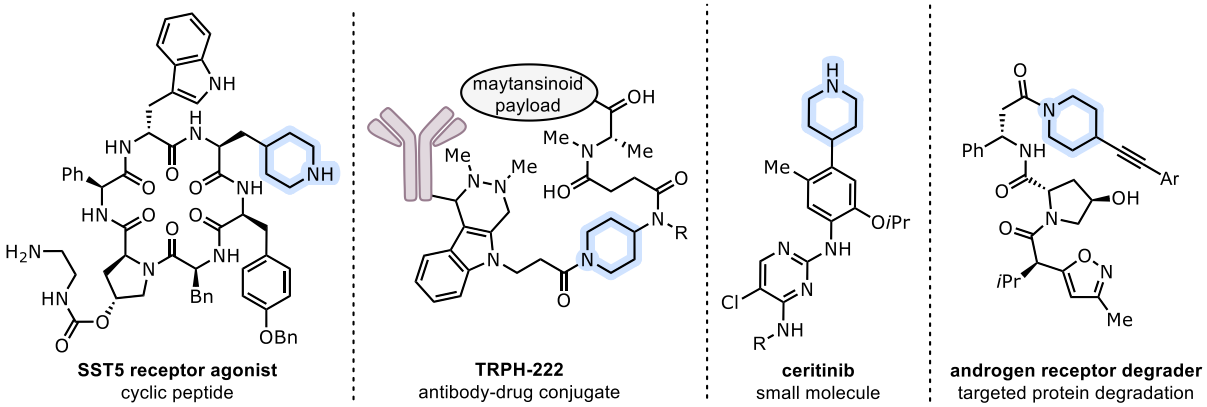


Figure 6: Different modalities of piperidine containing drugs.

These modalities include, but are not limited to, cyclic peptides, antibody-drug conjugates, small molecule drugs, and targeted protein degraders. In these cases, piperidine can play two different roles. It either acts as a primary pharmacophore (interacting with the target) or as a linker with predictable exit vectors and acceptable physiochemical properties. If, however, liabilities related to the piperidine core prevent candidate progression into preclinical development, or if fine-tuning of ADME (absorption, distribution, metabolism, excretion) profile is needed, bioisosteric replacement can be utilized.

2.1. (Bio)isosterism

The term "isostere" was coined by Langmuir in 1919 to describe molecules and ions with the same number and arrangement of electrons.[8] Since his pioneering work, the definition of isosteres changed throughout the following years (Table 1).

Table 1: Definitions of (bio)isosteres over time.

Author	Year	Definition
I. Langmuir	1919	Comolecules are isosteric if they contain the same number and arrangement of electrons.
H. G. Grimm	1925	Grimm's hydride displacement law: The addition of hydrogen to an atom will result in a pseudoatom with similar properties to the atom of the next highest atomic number.
F. Erlenmeyer	1932	Isosteres are elements, molecules or ions in which the peripheral layers of electrons may be considered identical.
H. L. Friedman	1951	Bioisosteres fit the broadest definition of isosteres and have the same type of biological activity.
C. W. Thornber	1979	Bioisosteres are groups or molecules which have chemical and physical similarities producing broadly similar biological properties.
A. Burger	1991	Bioisosteres are compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physicochemical properties.

Given the breadth of the latter definitions, the substitution of mono-, di-, tri- and tetra-substituted atoms, groups or even entire rings can be considered as a bioisosteric replacement. These substitutions can lead to profound changes in molecular structure (molecular size, bond angles), receptor interactions, pharmacokinetics, and metabolism.

Several notable examples of effective piperidine bioisosterism in drug discovery are presented below (Figure 7).

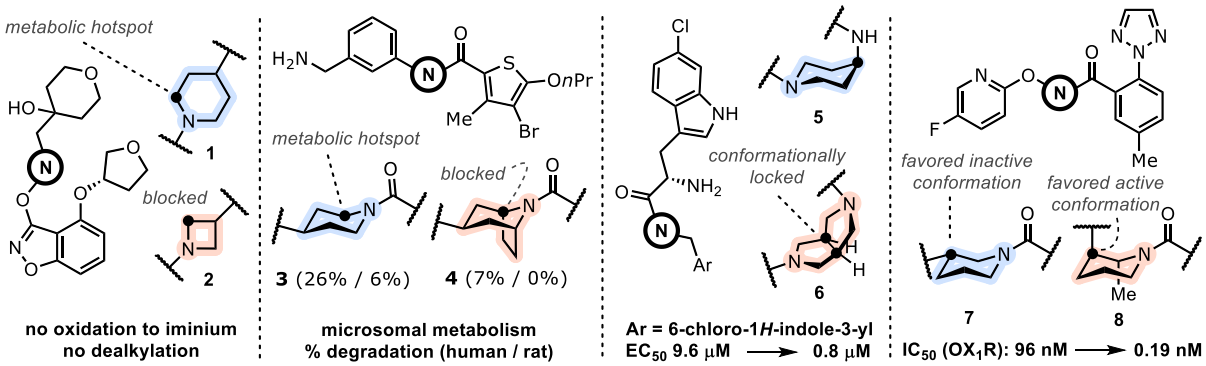


Figure 7: Selected examples of successful piperidine bioisosteres.

The Achilles heel of the piperidine substructure is the tertiary amine, which can be oxidatively metabolized by CYP450 enzymes, peroxidases, FMOs and MAOs.[9] Oxidation events (SET and HAT) give rise to iminium intermediates, which can be further hydrolyzed to give dealkylated products or be trapped by adventitious nucleophiles (Figure 8).

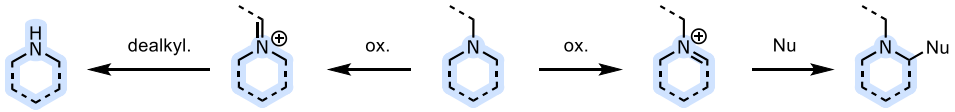


Figure 8: Oxidative metabolism of tertiary amines.

In the first example (Figure 7, far left), metabolism of the serotonin-4 partial agonists **1** and **2** shifted primarily from piperidine oxidation in **1** to oxazoline oxidation in azetidine isostere **2**.[9] This result was rationalized with the help of computational studies, which revealed that in the azetidine case, the energy barrier for hydrogen atom abstraction at the α-position is higher than in the piperidine case.

The same metabolic hotspot in the β-tryptase inhibitor **3** was blocked by the introduction of tropane bioisostere **4** (Figure 7, middle left).[10] This simple bioisosteric replacement led to significantly slower microsomal degradation (percentage of degraded compound after 20 min incubation with liver microsome fractions). This result was attributed to the increased rigidity of tropane scaffold and decreased chance of binding to the active sites of metabolic enzymes.

Cocrystal structure of piperidine **5** with SOS1 revealed that 4-amino substituent resides in axial position.[11] This conformation was computed to be 34 kcal/mol higher energy than the ground state conformation (Figure 7, middle right). To reduce this entropic penalty of binding, isostere **6** was introduced, which resulted in a 10-fold increase in potency.

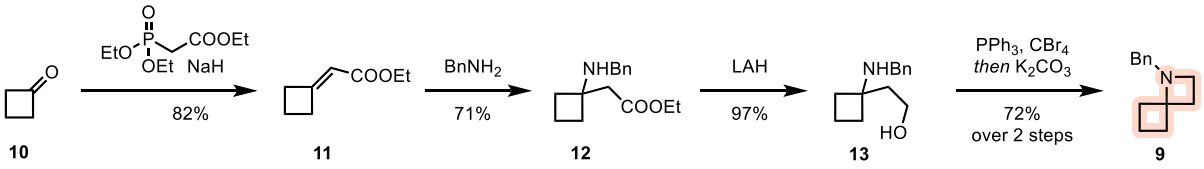
Last but not least, the case of orexin receptor agonist **7** convincingly demonstrates the importance of reducing the conformational flexibility of piperidines and addressing the problematic dilution of bioactive conformation for achieving high potency (Figure 7, far right).[12] Introduction of a single methyl group to the piperidine core led to bioisostere **8,** which has 505-times greater potency than its progenitor. Both NOE and X-ray analyses of relevant analogues revealed the preference for trans-

diaxial conformation, which is necessary for optimal binding to the target and which explains the origin of "the magic methyl effect".[13]

However, in none of examples of successful piperidine replacements is the carbon atom number conserved. Increased molecular weight, molecule surface area and lipophilicity can lead to off target toxicity.[14] An ideal piperidine bioisostere should therefore have the same number of carbon atoms. Since geometrical requirements vary from target to target, SAR studies are routinely performed during medicinal chemistry campaigns, and many piperidine isosteres are explored. While structurally most simplistic piperidine bioisosteres are azetidines, pyrrolidines and azepines, one can also envision more rigid and complex scaffolds like 2-azaspiro[3.3]heptanes, 3-azabicyclo[3.1.0]hexanes, 3-azabicyclo[3.2.0]heptanes, 2-azabicyclo[2.2.0]hexanes, etc. From a synthetic perspective, these scaffolds present different challenges, evident from the number of steps required for their preparation and the complexity/availability of their respective starting materials. Selected synthetic approaches towards these scaffolds and some uses in medicinal chemistry settings are presented in the following paragraphs.

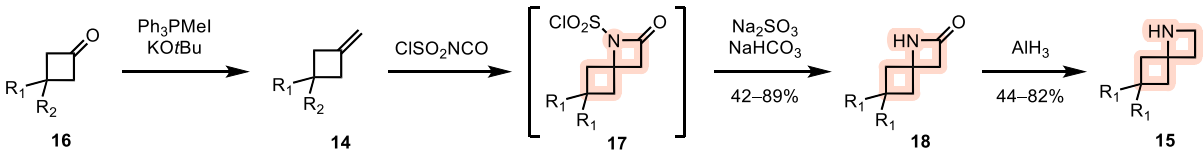
2.2. 1-azaspiro[3.3]heptanes

Carreira's group established access to unsubstituted 1-azaspiro[3.3]heptane **9** in 5 steps from commercially available cyclobutanone **10** (Scheme 1).[15] HWE olefination gave unsaturated ester **11** in 82% yield. Aza-Michael addition of benzylamine yielded secondary amine **12**. The protected amino alcohol **13** from LAH reduction step was sufficiently pure to be directly subjected to Appel reaction conditions without further purification. Upon completion, potassium carbonate was added to the reaction mixture, furnishing the final product **9** in 72% yield over two steps.



Scheme 1: Carreira's approach towards 1-azaspiro[3.3]heptanes.

Mykhailiuk's group recently explored the scope of [2+2] cycloaddition between methylenecyclobutanes **14** and chlorosulfonyl isocyanate for the synthesis of substituted 1-azaspiro[3.3]heptanes **15** (Scheme 2).[16] The majority of requisite substituted methylenecyclobutanes **14** were prepared via Witting olefination from the corresponding cyclobutanones **16**. Thermal [2+2] cycloaddition intermediates **17** were not isolated but were directly treated with sodium sulfite and sodium bicarbonate to give lactams **18** in 42–89% yields as 1 : 1 to 1 : 1.7 mixtures of diastereoisomers. Out of all reducing reagents tested, alane proved to be the best for reducing the the β-lactam moiety to furnish substituted 1-azaspiro[3.3]heptanes **15** as free amines**.** The substrate scope for this sequence of transformation (R_1 & R_2) features aliphatic and aromatic side chains as well as spirocycles. Esters and nitriles were reduced in the process to the corresponding alcohols and amines.



Scheme 2: Mykhailiuk's approach towards 1-azaspiro[3.3]heptanes.

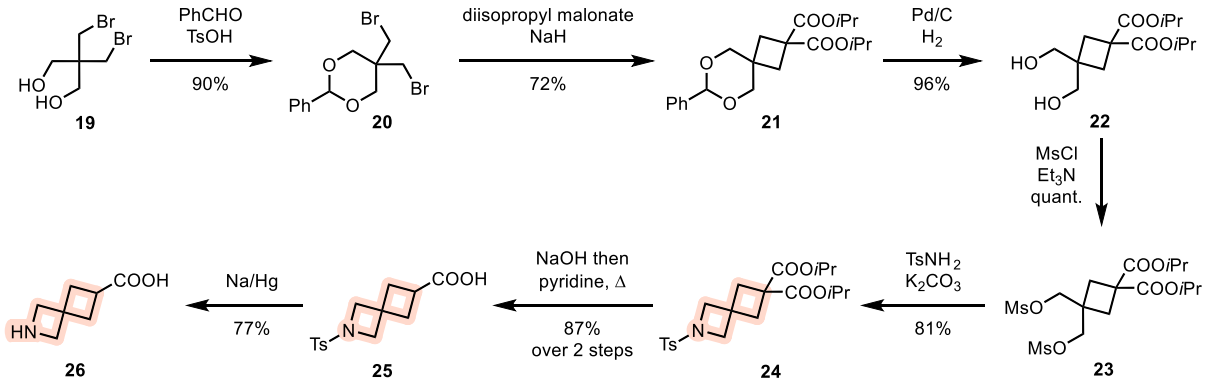
The 1-azaspiro[3.3]heptane moiety was examined in an SAR campaign dedicated to improving high-affinity poly(ADP-ribose) polymerase inhibitors (PARPi's) without DNA damaging properties.[17] In the

aforementioned case, FDA-approved Olaparib was chosen as a benchmark for assessing properties of synthesized bioisosteres.

2.3. 2-azaspiro[3.3]heptanes

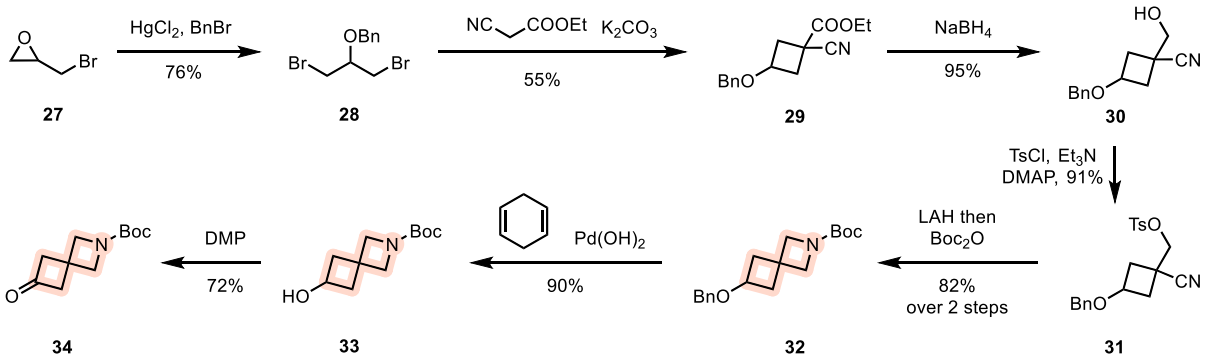
The SAR campaign described above also included the 2-azaspiro[3.3]heptane scaffold.[17] Additionally, it was shown to be a superior linker with increased metabolic stability for making orally bioavailable fetal hemoglobin (HbF) inducers intended for treating sickle cell disease.[18]

6-substituted 2-azaspiro[3.3]heptanes can be synthesized from commercially available 2,2-bis(bromomethyl)-1,3-propanediol **19** in 8 steps (Scheme 3).[19] Protection of both primary alcohols with benzaldehyde in the form of an acetal (**20**) is followed by double alkylation with diisopropyl malonate to give diester **21**. Deprotection with palladium on carbon and hydrogen gives diol **22**, which is mesylated to yield bis-mesylate **23**. The latter is treated with *p*-toluenesulfonamide and potassium carbonate to give 2-azaspiro[3.3]heptane **24**. Saponification and decarboxylation yield carboxylic acid **25** in 87% yield over two steps. Amino acid **26** can be prepared via sulfonamide deprotection using sodium amalgam.



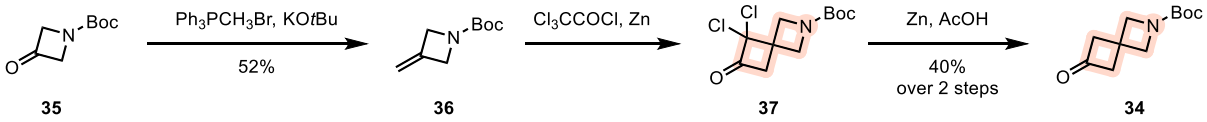
Scheme 3: Grygorenko's approach towards 2-azaspiro[3.3]heptanes.

A conceptually very similar approach was disclosed by Meyers et al. (Scheme 4).[20] Their synthesis starts with epibromohydrin **27**. Reaction with benzyl bromide in the presence of $HgCl_2$ gives dibromide **28**, which is used as an alkylating agent for ethyl cyanoacetate. Reduction of ester **29** with $NaBH_4$ gives alcohol **30**, which is then reacted with *p*-toluenesulfonyl chloride and Et_3N. When tosylate **31** is treated with LAH, a cascade of nitrile reduction and intramolecular *N*-alkylation occurs. Addition of Boc_2O to the reaction mixture gives carbamate **32** in 82% yield over three steps. Removal of the benzyl protecting group using Pearlman's catalyst and 1,4-cyclohexadiene as a hydrogen source gives alcohol **33**, which is then finally oxidized with DMP to give the final ketone **34**.



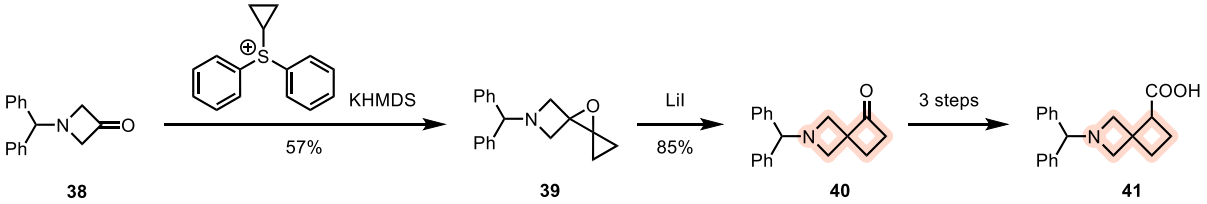
Scheme 4: Meyers' approach towards 2-azaspiro[3.3]heptanes.

The same group also reported a shorter, three-step route to the same ketone **34** (Scheme 5). Starting from *N*-Boc-azetidine-3-one **35**, Wittig olefination gives exocyclic olefin **36**, which is then exposed to *in situ* generated dichloroketene. Thermal [2+2] cycloaddition gives *gem*-dichloride **37**, which is finally reduced with zinc and acetic acid to produce spirocyclic ketone **34** in 40% yield over two steps.



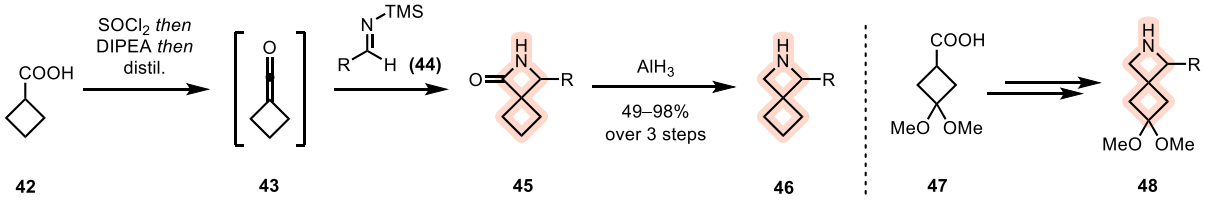
Scheme 5: A shorter route to 2-azaspiro[3.3]heptanes by Meyers.

An angular analogue of carboxylic acid **26** was prepared using Trost's cyclopropyldiphenylsulfonium ylide and subsequent rearrangement (Scheme 6).[21,22] Initial cyclopropanation of cyclobutanone **38** gives oxaspiropentane **39**, which can be converted to the final 2-azaspiro[3.3]heptane **40** with lithium iodide. This rearrangement can also be performed in one pot, albeit in a slightly lower yield. Three more steps involving ketone homologation, hydrolysis and oxidation are required to convert ketone **40** into carboxylic acid **41**.



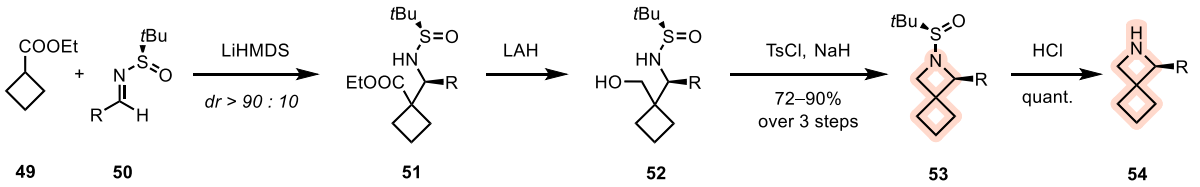
Scheme 6: Carreira's approach towards 2-azaspiro[3.3]heptanes.

Introduction of substituents at C1 position of the 2-azaspiro[3.3]heptane scaffold requires *de novo* synthesis from cyclobutanecarboxylic acid **42** (Scheme 7).[23] The acid is first converted into ketene **43** and then treated with *N*-silylated imines **44** (prepared in one step from aliphatic or aromatic aldehydes and KHMDS). Thermal [2+2] cycloaddition yields spirocyclic β-lactams **45**, which are finally reduced with alane to give the desired products **46**. The overall yields are fair to excellent despite the limited stability of ketene **43** and imines **44**. If an additional substituent at C6 position is desired, cyclobutanecarboxylic acid **42** can be replaced with its derivative **47** to give 2-azaspiro[3.3]heptanes **48** with two functional handles (amine and ketal moieties).



Scheme 7: Mykhailiuk's approach towards 2-azaspiro[3.3]heptanes.

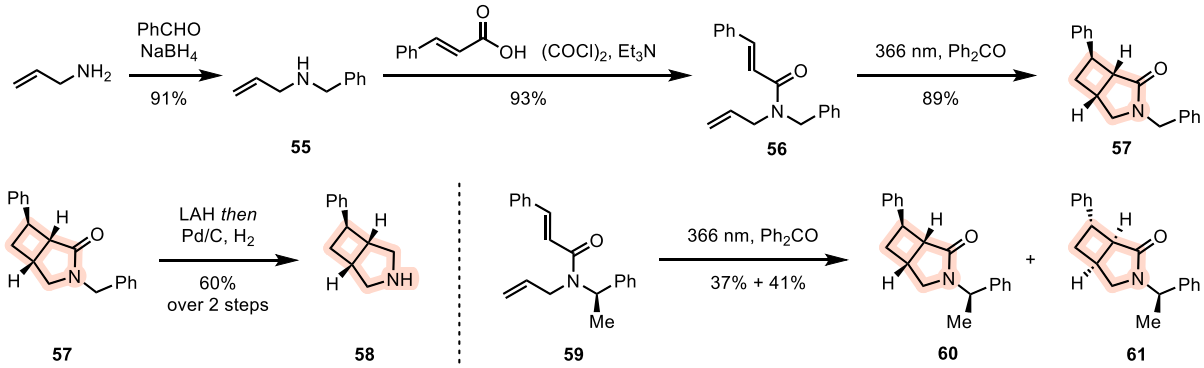
Enantioselective entry to 2-azaspiro[3.3]heptane bioisosteres was developed by Reddy et al.[24] *In situ* deprotonation of ester **49** and a 1,2-addition into *N-tert*-butanesulfinyl aldimines **50** gives alkylated esters **51** with *drs* > 9 : 1, which are subsequently reduced with LAH to the corresponding alcohols **52** (Scheme 8). Tosylation followed by intramolecular *N*-alkylation gives spirocyclic products **53** in good to excellent yields. Ellman's auxiliary can be removed afterward using HCl solution in dioxane to furnish the optically enriched 2-azaspiro[3.3]heptanes **54**. The substrate scope for these transformations is broad and, like the example above, aromatic aldehydes with different electronic properties are tolerated. A single example of an aliphatic aldehyde is disclosed as well.



Scheme 8: Reddy's approach towards 2-azaspiro[3.3]heptanes.

2.4. 3-azabicyclo[3.2.0]heptanes

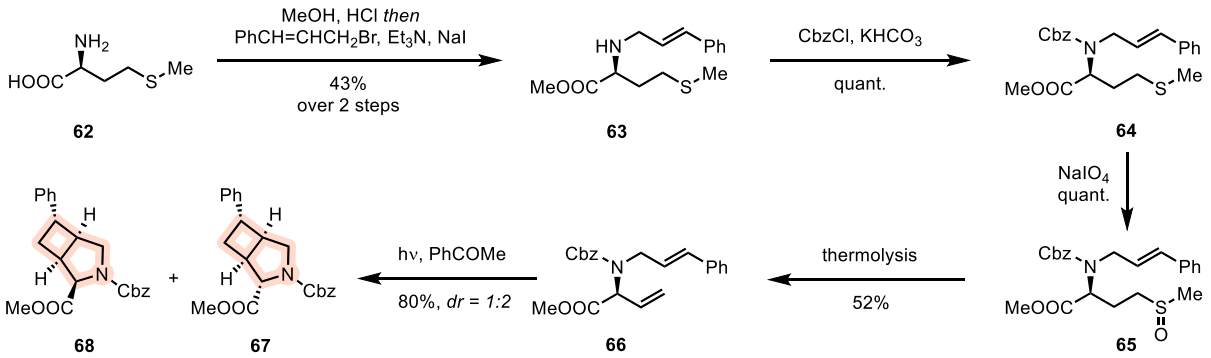
Mykhailiuk et al. used benzophenone as a photosensitizer to effect an intramolecular photochemical [2+2] cycloaddition and to synthesize 3-azabicyclo[3.2.0]heptane piperidine bioisosteres.[25] Their synthesis begins with reductive amination between allylamine and benzophenone to give secondary amine **55** (Scheme 9). Its acylation with cinnamic acid-derived acyl chloride yielded tertiary amide **56**, which was transformed into the desired bicyclic product **57** in 89% yield with UV irradiation. LAH reduction and palladium-catalyzed hydrogenolysis yielded synthetically tractable amine **58**. The authors showed that various cinnamic acid derivatives could be coupled with amine **55** and then transformed into the corresponding 3-azabicyclo[3.2.0]heptanes in good yields (61–89%). Additionally, access to optically pure 3-azabicyclo[3.2.0]heptanes was established by performing photochemical [2+2] cycloaddition with optically pure 1-phenylethylamine derived tertiary amide **59**. Diastereomeric products **60** and **61** were separated using conventional column chromatography and then following the same sequence of transformations converted to optically pure amines (*R*)-**58** and (*S*)-**58** (not drawn explicitly).



Scheme 9: Mykhailiuk's approach towards 3-azabicyclo[3.2.0]heptanes.

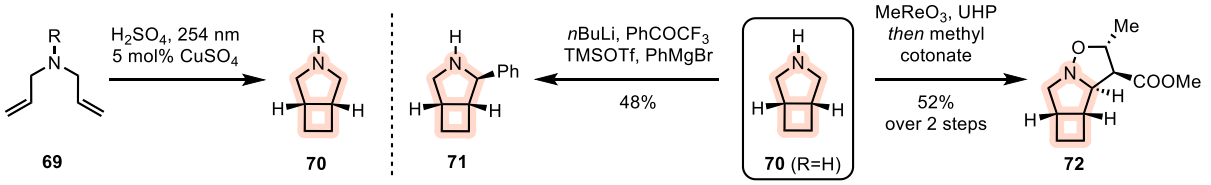
The groups of Cibulka and Yoon published similar photochemical [2+2] cycloadditions to access related products using flavine and $[Ir(^{F}ppy)2(t\text{Bubpy})]PF_6$ photocatalysts, respectively.[26,27]

To prepare 2-substituted-3-azabicyclo[3.2.0]heptane derivatives with a carboxylic acid functional handle, Bach et al. commenced their synthesis with amino acid methionine **62** (Scheme 10).[28] Fischer esterification and subsequent *N*-alkylation with cinnamyl bromide yielded amine **63**, which was then protected with CbzCl to give carbamate **64**. The methyl sulfide moiety was oxidized with sodium periodate to give sulfoxide **65** in quantitative yield. Vacuum thermolysis was challenging as it gave only a modest yield of the required diene **66** due to competing olefin isomerization. Finally, acetophenone sensitized photochemical [2+2] cycloaddition afforded a 2 : 1 mixture of diastereoisomers **67** and **68**.



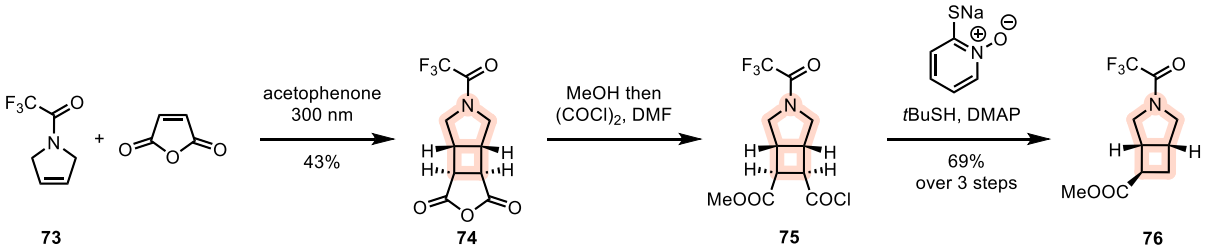
Scheme 10: Bach's approach towards 3-azabicyclo[3.2.0]heptanes.

In their recent publication, Burns' group demonstrated that diallylamines **69** could undergo photochemical [2+2] cycloaddition with catalytic amounts of $CuSO_4$ in aqueous media using a 254 nm light source (Scheme 11).[29] Various groups on the nitrogen atom (alkyl, acyl, sulfonyl) are tolerated under these conditions and yields are consistently high (>71%). Furthermore, even free diallylamine **69** (R=H) undergoes a successful [2+2] cycloaddition in 82% yield. Instead of bringing in substituents with their cyclization precursors **69**, the authors decided to introduce them at a later stage. Thus, unprotected 3-azabicyclo[3.2.0]heptane (**70**) was exposed to Seidel's α-functionalization conditions to diastereoselectively install a phenyl group at the C2-position (bicycle **71**) in 48% yield. Alternatively, the C2-position could be formally alkylated via a [3+2] cycloaddition between methyl crotonate and the respective nitrone (not shown) to give tricycle **72**.



Scheme 11: Burns' approach towards 3-azabicyclo[3.2.0]heptanes.

An alternative disconnection for making 3-azabicyclo[3.2.0]heptanes, which relies on an intramolecular [2+2] cycloaddition rather than an intermolecular [2+2] cycloaddition, can also be envisioned. Wanner et al. utilized maleic anhydride and *N*-(trifluoroacetyl)-3-pyrroline (**73**), which reacted under photochemical conditions with acetophenone as a photosensitizer to give tricycle **74** in 43% yield (Scheme 12).[30] Subsequent treatment with methanol and oxalyl chloride in the presence of DMF furnished acyl chloride **75**. The latter was immediately subjected to the Barton decarboxylation protocol to yield methyl ester **76** in 69% yield over three steps.

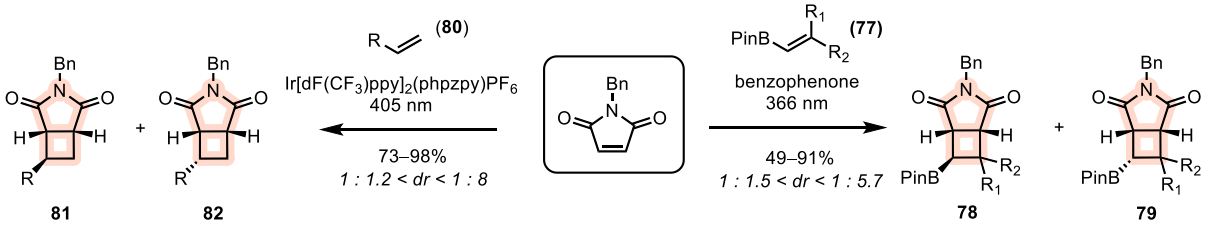


Scheme 12: Wanner's approach towards 3-azabicyclo[3.2.0]heptanes.

By replacing maleic anhydride with *N*-benzylmaleimide, 3-pyrroline **73** with vinylboronic acid pinacol esters (**77**) and acetophenone with benzophenone, the Grygorenko's group gained access to 3-azabicyclo[3.2.0]heptanes with a boronic ester functional handle at the C6-position (compounds **78**

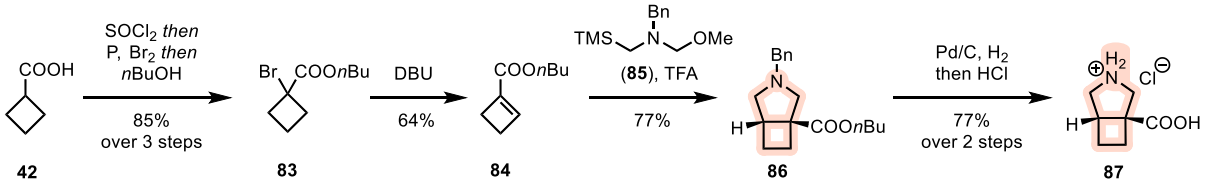
and **79**, Scheme 13, right).[31] While the synthetic potential of the aforementioned functional handle is large, the substrate scope of vinylboronic acid esters **77** is substantial and yields of the [2+2] photocycloaddition are generally modest to excellent, this methodology is plagued by poor diastereoselectivity as mixtures of difficult-to-separate exo- (**78**) and endo-isomers (**79**) are formed.

The use of an iridium photocatalyst $Ir[dF(CF_3)ppy]_2(phpzpy)PF_6$ allowed Liu et at. to shift the photosensitized [2+2] cycloaddition with the *N*-benzyl maleimide from the ultraviolet to visible region (Scheme 13, left).[32] A broad range of olefins **80** was tolerated in this transformation, which gave rise to a library of substituted 3-azabicyclo[3.2.0]heptanes. Specifically, acrylamides, acrylates, enones, styrenes, enamides, vinyl sulfides, enol ethers, enol acetates, vinyl and allyl silanes all gave excellent yields of the desired products **81** and **82**. However, just like in Grygorenko's case, the diastereoselectivity of this transformation is generally poor, with the *exo*-isomer **81** being the major one.



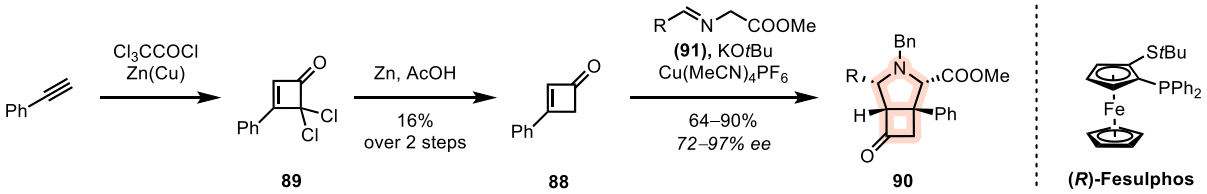
Scheme 13: Liu's (left) and Grygorenko's (right) approaches towards 3-azabicyclo[3.2.0]heptanes.

Photochemical [2+2] cycloadditions are not the only way to access 3-azabicyclo[3.2.0]heptanes as 1,3-dipolar cycloaddition can be used instead (Scheme 14).[33] Starting from commercially available cyclobutanecarboxylic acid **42**, a sequence of chlorination, Hell-Volhard-Zelinsky reaction and *n*-butyl ester formation gives α-bromoester **83** in 85% yield over 3 steps. DBU mediated elimination yields unsaturated ester **84** in 64% yield. The required intermediate azomethine ylide (not shown) is formed *in situ* via the reaction between hemiaminal **85** and TFA, which then reacts with the unsaturated ester **84** to yield the desired product **86** in 77% yield. A two-step deprotection sequence consisting of palladium-catalyzed hydrogenolysis and acid-catalyzed ester hydrolysis yields the hydrochloride salt of unnatural amino acid **87**.



Scheme 14: Grygorenko's 1,3-dipolar cycloaddition approach towards 3-azabicyclo[3.2.0]heptanes.

The aforementioned 1,3-dipolar cycloaddition can also be performed in an enantioselective fashion by using catalytic amounts of $Cu(MeCN)_4PF_6$ and (*R*)-Fesulphos ligand (Scheme 15).[34] The requisite enone **88** for the cycloaddition is prepared in two steps from phenylacetylene via thermal [2+2] cycloaddition with dichloroketene (yielding *gem*-dichloride **89**), followed by zinc-mediated dechlorination in 16% yield over two steps. The dipolar cycloaddition then gives good to excellent yields of desired products **90**, regardless of specific glycine imines **91** used and with perfect diastereoselectivity. Enantiomeric access is uniformly high (72–97% *ee*) in these cases, and the products **90** have, besides the ester functionality, an additional ketone functional handle at C6-position.

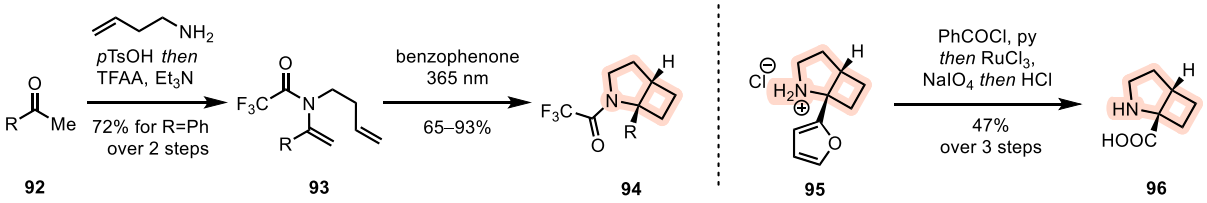


Scheme 15: Adrio's and Carretero's asymmetric 1,3-dipolar cycloaddition approach towards 3-azabicyclo[3.2.0]heptanes.

Derivatives of the 3-azabicyclo[3.2.0]heptane skeleton were shown to be both competent ligands for dopaminergic receptors[35] as well as having morphine-like analgesic activity[36].

2.5. 2-azabicyclo[3.2.0]heptanes

2-azabicyclo[3.2.0]heptanes are synthesized using the same retrosynthetic logic (Scheme 16).[37] First, a variety of aryl methyl ketones **92** are condensed with homoallyl amine. A judicious choice of base is then required to prepare protected enamides **93** without competing electrophilic substitution with trifluoroacetic anhydride. Photochemical [2+2] head-to-head cycloaddition in the presence of benzophenone then furnishes desired products **94** in 65–93% yields. Since only aryl methyl ketones **92** were shown to be competent substrates for the described sequence of transformations, 1-furan-2-yl substituted 2-azabicyclo[3.2.0]heptane **95** was transformed into amino acid **96** via amine acylation, ruthenium tetroxide furane oxidation, and amide hydrolysis in 47% yield over three steps.

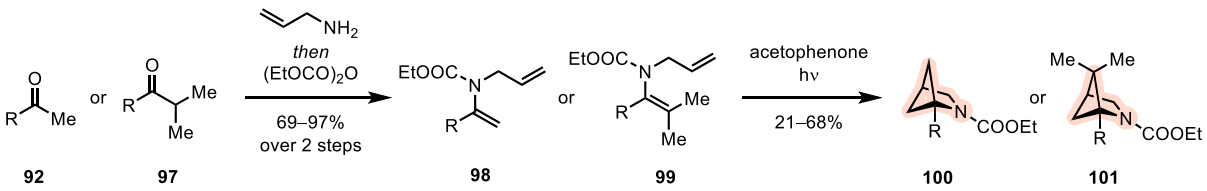


Scheme 16: Mykhailiuk's approach towards 2-azabicyclo[3.2.0]heptanes.

The use of 2-azabicyclo[3.2.0]heptanes in a medicinal chemistry setting for synthesizing modulators of cystic fibrosis transmembrane conductance regulators is described in patents.[38]

2.6. 2-azabicyclo[2.1.1]hexanes

When allylamine is used instead of homoallyl amine in combination with methyl aryl ketones **92** or isopropyl aryl ketones **97** for the preparation of enecarbamates **98** and **99**, the ensuing photochemical [2+2] cycloaddition proceeds in a head-to-tail fashion, yielding 2-azabicyclo[2.1.1]hexanes (**100** and **101**) instead (Scheme 17).[39] The reported yields are in the 21–68% range. Although both electron-rich and electron-deficient aryl methyl ketones can be used, the final products offer little opportunities for further derivatization of the core.



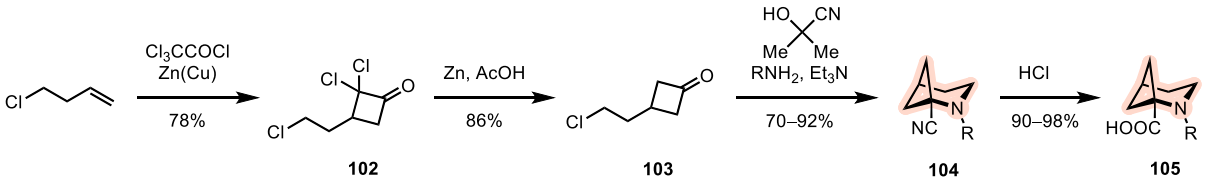
Scheme 17: Piotrowski's approach towards 2-azabicyclo[2.1.1]hexanes.

It was later discovered that ethyl pyruvate can be used instead of aryl methyl ketones **92**.[40] A similar sequence of transformations to those described above gave 2-azabicyclo[2.1.1]hexane **100** with a carboxyethyl functional handle (R = COOEt; NCOPh instead of NCOOEt). This compound served as a

precursor to novel nicotinic acetylcholine receptor ligands, which, however, proved to display incompetent binding.[41]

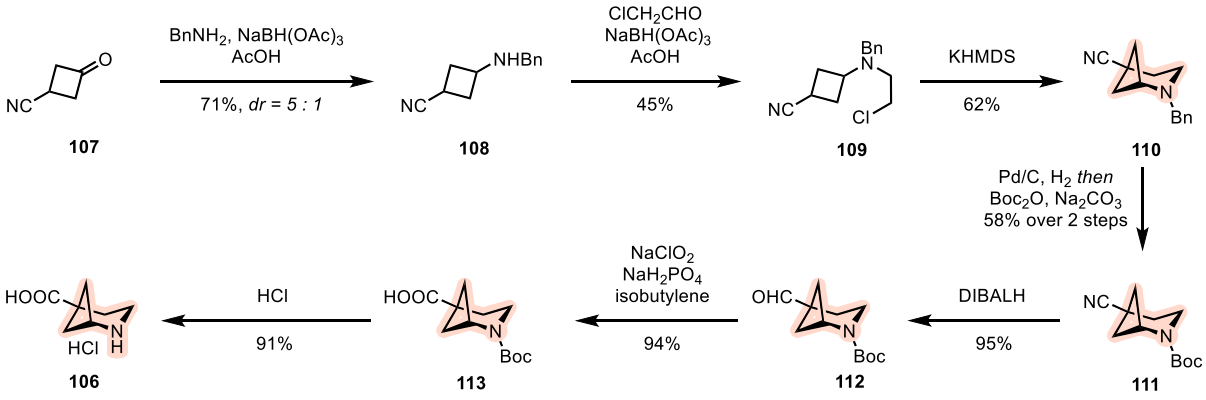
2.7. 2-azabicyclo[3.1.1]heptanes

Stevens et al. build their 2-azabicyclo[3.1.1]heptane isosteres from homoallyl chloride (Scheme 18).[42] Thermal [2+2] cycloaddition with *in situ* generated dichloroketene yielded cyclobutanone **102**, which was dechlorinated with zinc in acetic acid to give cyclization precursor **103** in 67% yield over two steps. The latter was exposed to a variety of primary amines (RNH_2) as well as triethylamine and acetone cyanohydrin as the cyanide source to effect a tandem Strecker-intramolecular cyclization reaction and to give bicycles **104**. The nitrile group was then hydrolyzed with hydrochloric acid to give protected amino acids **105** in excellent yields. While only aliphatic amines are tolerated in their key step, the use of benzylamine allowed for final amine deprotection (R = Bn) under hydrogenolytic conditions (not shown).



Scheme 18: Stevens' approach towards 2-azabicyclo[3.1.1]heptanes.

The 2-azabicyclo[3.1.1]heptane derivative with a carboxylic acid at C5-position **106** was prepared from 3-oxocyclobutane-1-carbonitrile **107** in 8 steps (Scheme 19).[43] Reductive amination between ketone **107** and benzylamine gave a mixture of amines **108** with 5 : 1 *dr*. A second reductive amination with chloroacetaldehyde gave primary chloride **109**, which underwent intramolecular cyclization with KHMDS to give nitrile **110**. The 2-azabicyclo[3.1.1]heptane core was thus built in four steps. Four additional steps focused on protecting group manipulations and redox adjustments. Specifically, the benzyl protecting group was removed with hydrogen and palladium on carbon and replaced with a *tert*-butyl carbamate **111** in 58% yield over three steps. DIBALH was used to reduce the nitrile group to the aldehyde **112**, which was reoxidized back to carboxylic acid **113** under Pinnick conditions. Final deprotection of *tert*-butyloxycarbonyl group was achieved with hydrochloric acid in 91% yield.

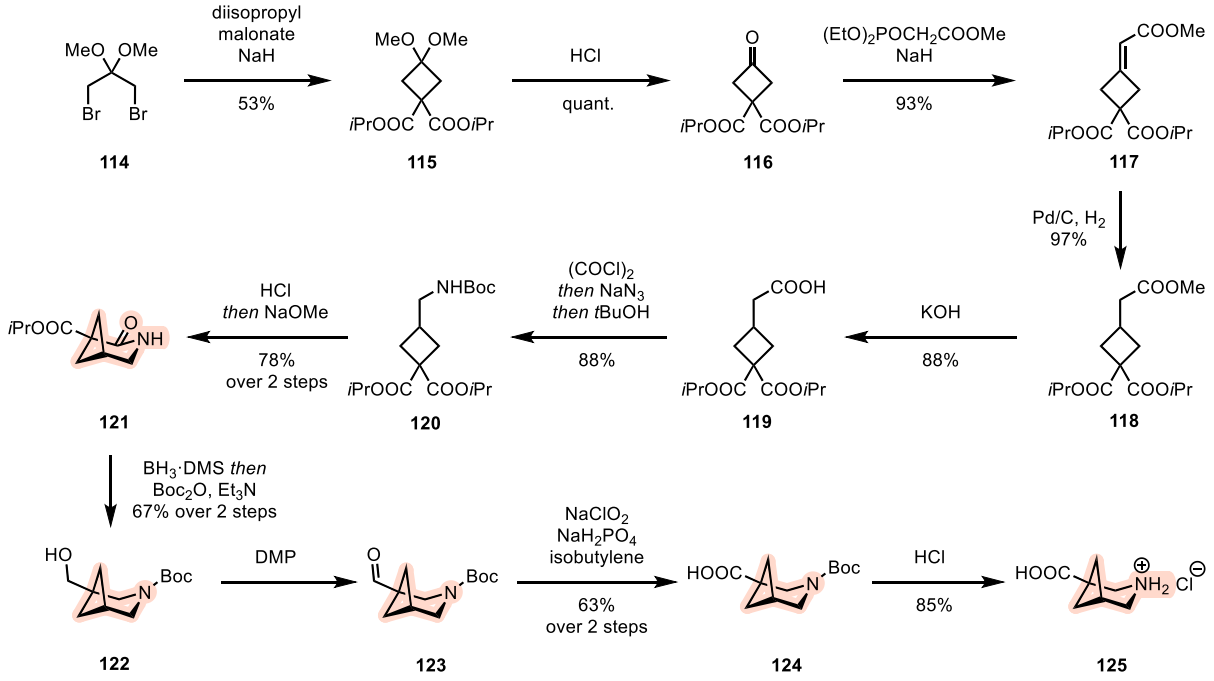


Scheme 19: He's approach towards 2-azabicyclo[3.1.1]heptanes.

The use of 2-azabicyclo[3.1.1]heptane derivatives as agonists of orexin-1/2 receptors has been patented.[44]

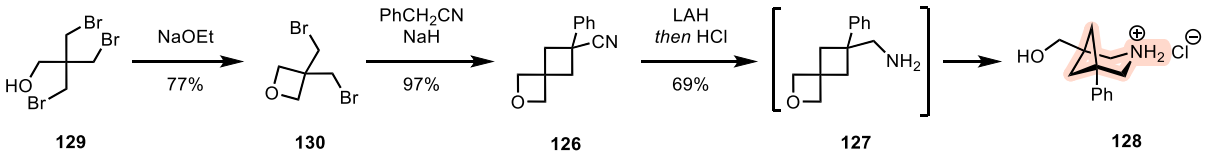
2.8. 3-azabicyclo[3.1.1]heptanes

A symmetry-inspired approach to 3-azabicyclo[3.1.1]heptanes is depicted in the next scheme (Scheme 20).[45] Dibromide **114** is reacted with diisopropyl malonate to give diester **115** in 53% yield. Dimethyl ketal is hydrolyzed with hydrochloric acid to give ketone **116,** which is then subjected to HWE olefination to yield unsaturated triester **117**. The double bond is afterwards hydrogenated with palladium on carbon and hydrogen to yield fully saturated triester **118**. Selective saponification with potassium hydroxide gives carboxylic acid **119**, which is then transformed into *tert*-butyl carbamate **120** in 88% yield by utilizing the venerable Curtius rearrangement. A two-step process consisting of carbamate deprotection and intramolecular lactamization is then carried out to give the 3-azabicyclo[3.1.1]heptane core **121**. Global reduction with borane dimethyl sulfide complex reduced both the isopropyl ester and the lactam to give, after amine reprotection, alcohol **122** in 67% yield. DMP oxidation then furnished aldehyde **123**, which itself can serve as a useful building block. The aldehyde was immediately oxidized under Pinnick conditions to yield acid **124** in 63% yield over 2 steps. Final deprotection with hydrochloric acid gives amino acid **125** as a hydrochloride salt.



Scheme 20: Mykhailiuk's approach towards 3-azabicyclo[3.1.1]heptanes.

A significantly shorter route to 3-azabicyclo[3.1.1]heptanes was discovered serendipitously (Scheme 21).[46] When LAH reduction of nitrile **126** was attempted, none of the desired amine **127** was obtained. Instead, hydroxymethylene substituted 3-azabicyclo[3.1.1]heptane **128** was formed (isolated as the corresponding hydrochloride salt in 69% yield). Nitrile reduction could also be accomplished with $NaBH_4$-$CoCl_2$ system, albeit in a slightly lower yield. Nitrile **126** was obtained in two steps from commercially available tribromide **129** via intramolecular Williamson etherification and isolable oxetane **130**, which was subsequently used to alkylate benzyl cyanide. The same sequence of transformations could be repeated with a wide range of nitriles with a general formula of R–CH_2–CN, where R is aryl, alkyl or a carboxylic acid derivative with yields in 35–89% range.

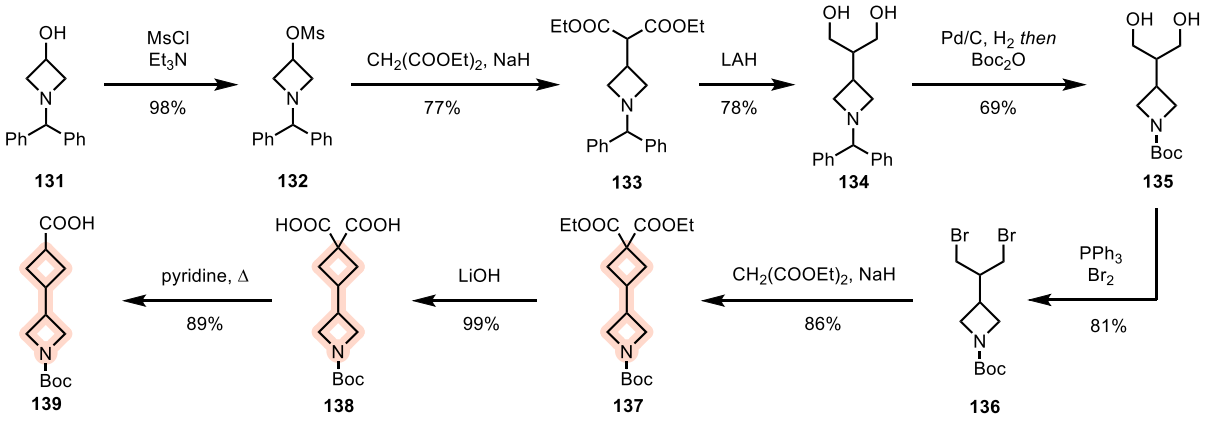


Scheme 21: A more concise approach towards 3-azabicyclo[3.1.1]heptanes by Mykhailiuk et al.

Higher oxidation state derivatives of 3-azabicyclo[3.1.1]heptane were successfully tested in vitro as inhibitors of human placental aromatase.[47]

2.9. 3-cyclobutylazetidines

3-cyclobutylazetidines represent a unique class of elongated piperidine isosteres, and their synthesis is depicted in the following scheme (Scheme 22).[48] Mesylation of commercially available alcohol **131** furnished mesylate **132** in an almost quantitative yield. The mesylate was then displaced with diethyl malonate anion to give diester **133**. Both ester groups were reduced with LAH in a single operation to give diol **134** in 78% yield. A two-step protecting group exchange maneuver with hydrogenolysis and carbamate installation furnished *tert*-butyl carbamate **135** in 69% yield. Double Appel reaction gave dibromide **136**, which was used to alkylate deprotonated diethyl malonate and establish the 3-cyclobutylazetidine core (diester **137**). Ester saponification gave diacid **138** quantitatively, which underwent thermal decarboxylation in the presence of pyridine to yield a useful building block **139** in 89% yield, albeit as a 1 : 1 mixture of diastereoisomers.



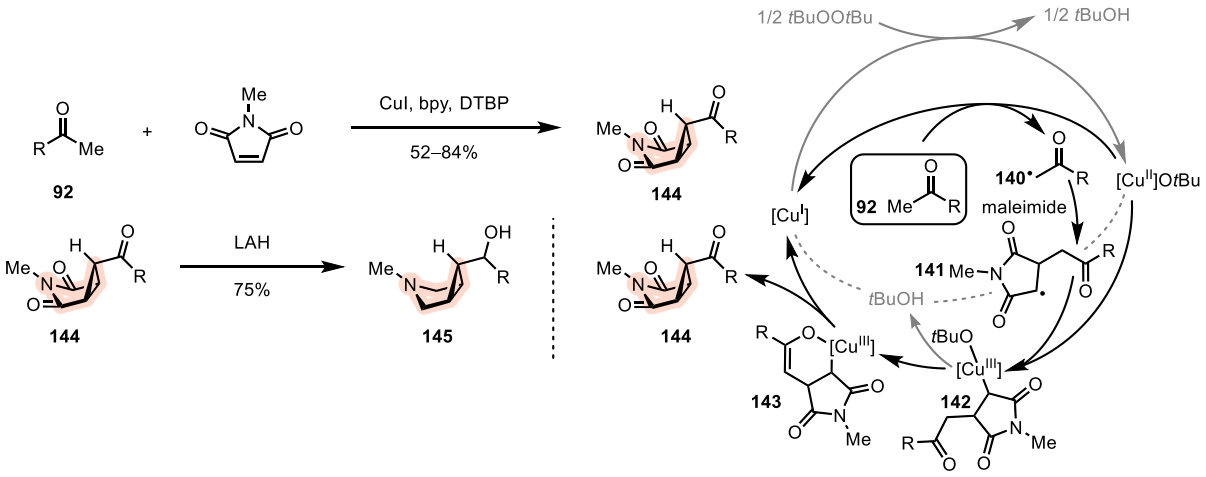
Scheme 22: Grygorenko's approach towards 3-cyclobutylazetidines

Literature describing the pharmacokinetic properties of 3-cyclobutylazetidine-containing drugs and drug candidates is limited, presumably due to their relative novelty as piperidine isosteres. However, examples can be found in patents.[49]

2.10. 3-azabicyclo[3.1.0]hexanes

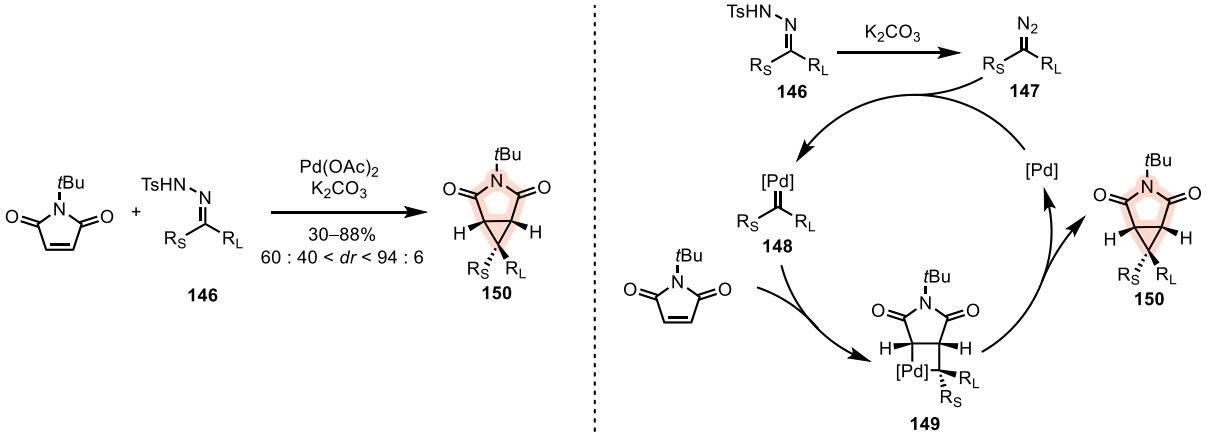
Fair to excellent yields of 3-azabicyclo[3.1.0]hexanes can be obtained via copper-catalyzed (2+1) annulation between aryl methyl ketones **92** and *N*-methylmaleimide with di-*tert*-butylperoxide (DTBP) acting as the terminal oxidant (Scheme 23).[50] A limited range of substituents on the aryl ring is tolerated (halides, esters, nitro groups, nitriles). The proposed reaction mechanism starts with the oxidation of [Cu^{I}] to [Cu^{II}]O*t*Bu species, which subsequently oxidizes ketone **92** to α-acyl radical **140**. This then adds across the double bond of *N*-methylmaleimide, giving rise to intermediate **141**, which is intercepted with [Cu^{II}]O*t*Bu species to give [Cu^{III}] species **142**. After enolization and ligand exchange intermediate **143** is formed, which, after reductive elimination, collapses to the final product **144** while

regenerating [Cu^{I}] species. Global reduction of ketone **144** with LAH furnishes amino alcohol **145** in 75% yield.



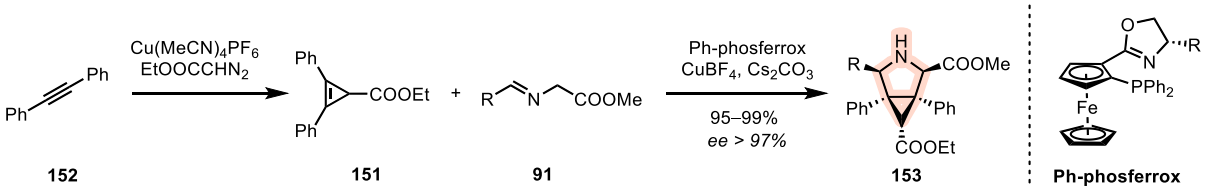
Scheme 23: Antonchick's approach towards 3-azabicyclo[3.1.0]hexanes.

Another (2+1) annulation with *N-tert*-butylmaleimide was developed to access racemic 3-azabicyclo[3.1.0]hexanes (Scheme 24).[51] A wide range of tosylhydrazones **146** derived from aromatic ketones was reacted with *N-tert*-butylmaleimide in the presence of catalytic amounts of palladium(II) acetate and superstoichiometric amounts of potassium carbonate as a base. Aromatic ketones bearing substituents like halides, esters, nitro groups, methyl ethers, thioethers, and trifluoromethyl groups are all well accommodated. Diazo compounds **147**, which are formed *in situ*, react with palladium(II) acetate to form palladium carbenoid species **148**. Afterwards, a 4-membered palladacycle **149** with the larger substituent R_L pointing away from the maleimide moiety forms preferentially. Reductive elimination then gives final products **150**. The obtained yields are in the 30-88% range and diastereoselectivities vary from 60 : 40 to 94 : 6.



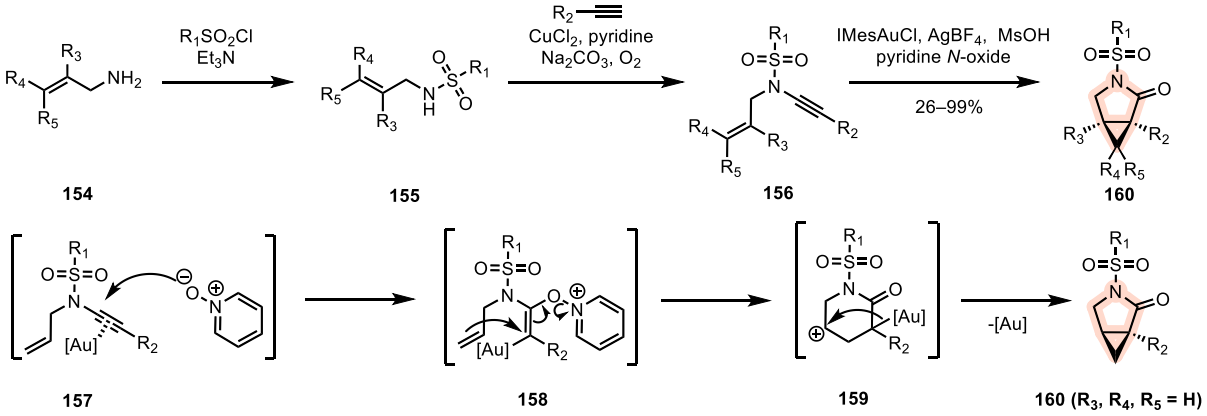
Scheme 24: Wu and Jiang's approach towards 3-azabicyclo[3.1.0]hexanes.

Asymmetric synthesis of 3-azabicyclo[3.1.0]hexanes was made possible by the development of copper-catalyzed [3+2] cycloaddition between cyclopropenes **151** and glycine imine derived azomethine ylide precursors **91** using Ph-phosferrox as a ligand (Scheme 25).[52] While yields and enantioselectivities are excellent regardless of the R group of glycine imines **91**, the reaction scope is limited to symmetrical substrates. Cyclopropenes **151** were synthesized from diphenylacetylene **152** and then converted to 3-azabicyclo[3.1.0]hexanes **153** equipped with two alkoxylcarbonyl functional handles.



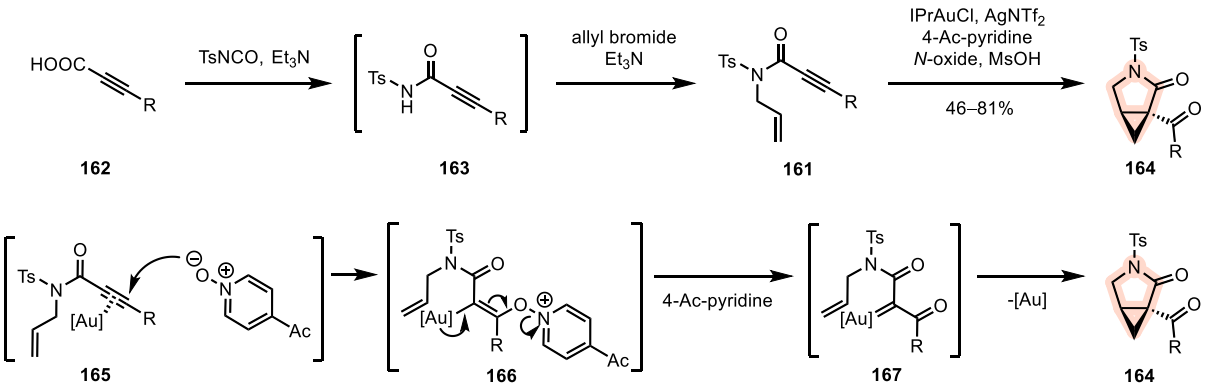
Scheme 25: Yang and Deng's asymmetric approach towards 3-azabicyclo[3.1.0]hexanes.

Li et al. developed a linear approach for synthesizing the 3-azabicyclo[3.1.0]hexane core (Scheme 26).[53] Firstly, substituted allyl amines **154** are protected with a variety of sulfonyl chlorides (R_1SO_2Cl) to yield sulfonamides **155**. Secondly, a copper-catalyzed oxidative coupling with terminal alkynes (R_2CCH) is performed to access ynamides **156**. Substrates bearing ester or ketone moieties (R_2 = COOEt, COMe, COPh) can also be prepared, although a different synthetic approach is required. Thirdly, these ynamides are cyclized in the presence of IMesAuCl complex, silver tetrafluoroborate, and pyridine *N*-oxide to give final products in 26–99% yields. According to the authors, the most probable mechanism for the last step involves the coordination of active gold species to the alkyne moiety of the substrate to form complex **157**, which is then attacked by pyridine *N*-oxide to give intermediate **158**. Subsequent 6-endo-trig cyclization forms carbocation **159**, which is intercepted by the carbon–gold bond to give the desired product **160**, thereby releasing the active gold species. The same transformation can also be catalyzed with copper, rhodium, or an organic photocatalyst.[54–56]



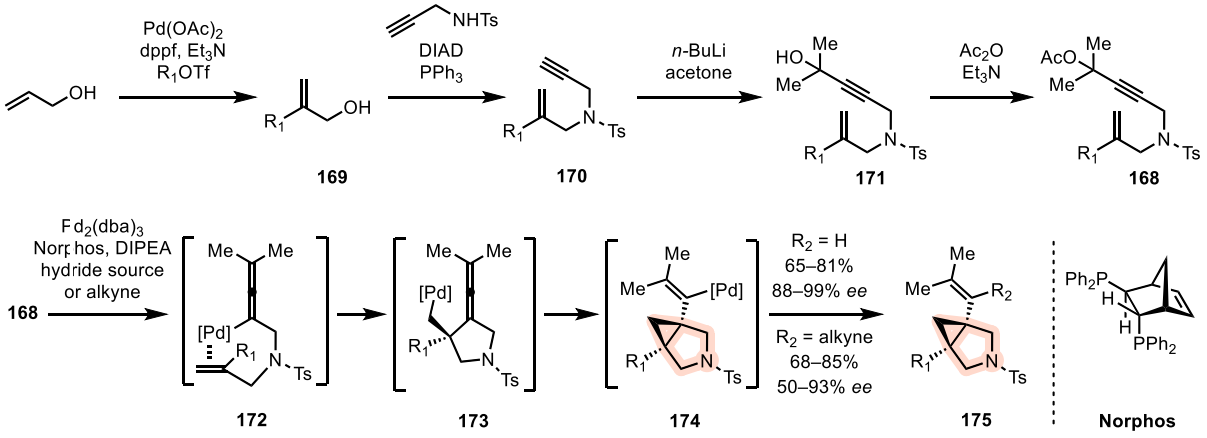
Scheme 26: Li's approach towards 3-azabicyclo[3.1.0]hexanes.

Gold catalysis can also be used to prepare 3-azabicyclo[3.1.0]hexanes with a similar substitution pattern from alkylated *N*-tosylpropiolamides **161** (Scheme 27).[57] These can be prepared in a two-step, one-pot operation from the corresponding propiolic acids **162** via alkylation of intermediate *N*-tosylpropiolamides **163**. 4-acetylpyridine-*N*-oxide is used as the terminal oxidant in the final cyclization step, which yields 3-azabicyclo[3.1.0]hexanes **164** in 46–81% yields. Propiolic acids adorned with electron deficient arenes do not seem to be tolerated. The proposed mechanism starts with the attack of the aforementioned *N*-oxide to the gold-coordinated substrate **165** to give intermediate **166**. Electron donation from gold results in the expulsion of 4-acetylpyridine. Finally, α-oxo gold carbenoid species **167** undergoes intramolecular cyclopropanation to furnish the desired products while closing the catalytic cycle.



Scheme 27: Zhang's approach towards 3-azabicyclo[3.1.0]hexanes.

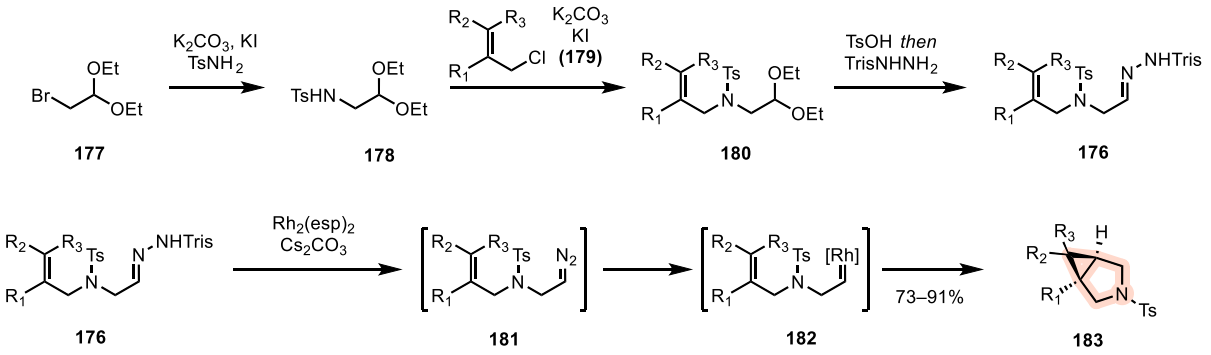
Protected allyl-propargyl-amines **168** can be transformed into 3-azabicyclo[3.1.0]hexanes enantioselectively (Scheme 28).[58] Starting with allyl alcohol, a Heck reaction is used to install aryl substituents (R_1) at the C2-position of alcohols **169**. Mitsunobu reaction with *N*-tosylpropargylamine yields sulfonamides **170**. Terminal acetylenes are deprotonated with *n*-BuLi and added into acetone to give tertiary alcohols **171**. Hydroxy groups are acylated under standard reaction conditions with acetic anhydride and triethylamine to give the cyclization precursors **168**. Cyclization then occurs in the presence of $Pd_2(dba)_3$, Norphos ligand, Hünig's base, and a hydride source (R_2 = H) or an alkyne. Silanes seem to be the most effective hydride source in this specific transformation. The reaction starts with a Pd(0) species undergoing oxidative addition to give intermediate **172**. Migratory insertion results in the formation of neopentylic alkyl palladium(II) species **173**, which undergoes a second migratory insertion to give the 3-azabicyclo[3.1.0]hexane intermediate **174**. Final reductive elimination with a hydride or acetylide gives the desired products **175** in 65–81% yields and 88–99% *ee* with silanes and 68–85% yields and 50–93% *ee* with alkynes. Instead of using palladium, this reaction can also be performed with superstoichiometric amounts of $TiCl_4$ (R_2 = Cl) or catalytically with calcium or ruthenium catalysts on related free tertiary alcohols in a racemic fashion (not shown).[59,60]



Scheme 28: Zhou's asymmetric approach towards 3-azabicyclo[3.1.0]hexanes.

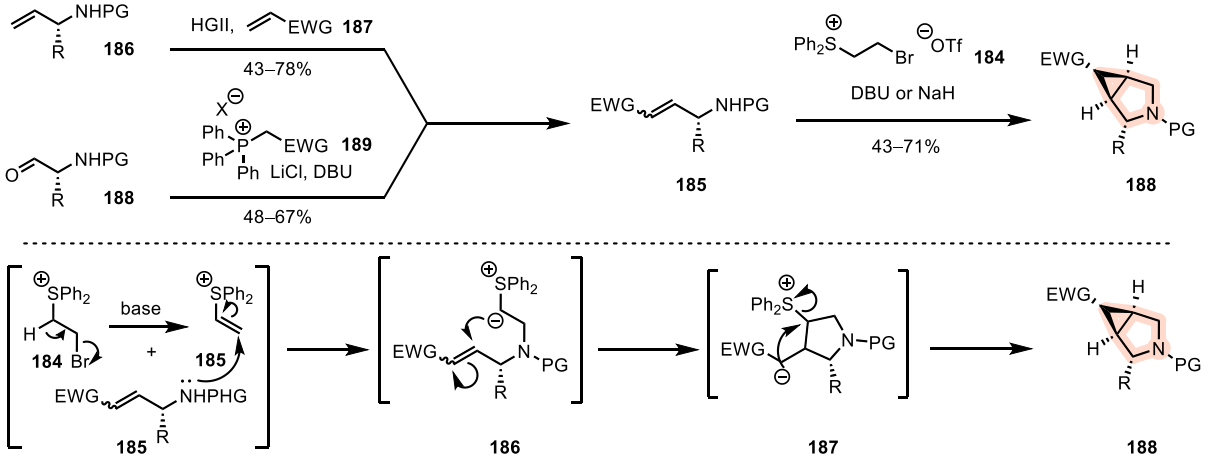
Rhodium-catalyzed cyclopropanation of suitable hydrazone precursors **176** presents a convenient way of synthesizing racemic 3-azabicyclo[3.1.0]hexanes (Scheme 29).[61] The synthesis of the precursors mentioned above starts from 2-bromoacetaldehyde diethyl acetal **177**. Alkylation with *p*-toluenesulfonamide gives *N*-alkylated sulfonamide **178**. A variety of different allylic chlorides (**179**) can then be used in the following alkylation that gives penultimate precursors **180**. Acetal hydrolysis and condensation with trisylhydrazide gives trisylhydrazones **176**. These were shown to be superior to all other tested hydrazones. The proposed mechanism for this reaction begins with the formation

of diazo species **181**, which is then transformed into rhodium carbenoid **182,** which does the intramolecular cyclopropanation and furnishes the final products **183**. While the yields for the synthesis of cyclization precursors are not reported, the yields for the subsequent rhodium catalyzed cyclopropanation lie in 73–91% range. Chiral rhodium catalysts that were evaluated gave synthetically impractical enantioselectivities up to 43% *ee*.



Scheme 29: Wang and Zhou's rhodium catalyzed approach towards 3-azabicyclo[3.1.0]hexanes.

Aggarwal's group developed a transition metal-free synthesis of 3-azabicyclo[3.1.0]hexanes with an electron-withdrawing group attached at the C6-position from commercially available sulfonium salt **184** and electron-deficient allylic amines **185** (Scheme 30).[62] These were in turn prepared from allylic amines **186** and electron-deficient olefins **187** with cross metathesis or from amino acid derived α-aminoaldehydes **188** and phosphonium salts **189** with the Masamune-Roush modification of the HWE reaction. The cyclization reaction presumably begins by elimination of hydrogen bromide from the sulfonium salt **184** to give Michael acceptor **185**. The latter is attacked by allylic amines **185**. Sulfonium ylides **186** thus formed undergo intramolecular Michael addition. Stabilized anion **187** then displaces diphenyl sulfide to give the final products **188**. Esters, nitriles, ketones and Weinreb amides are all tolerated, yielding the desired products in 43–71% yields and with perfect diastereoselectivity. Substrates derived from optically pure starting materials also give enantioenriched products without significant racemization.



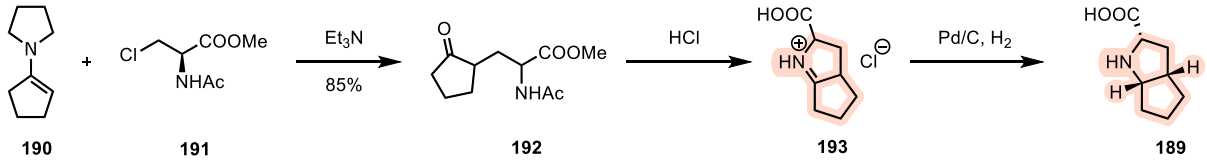
Scheme 30: Aggarwal's approach towards 3-azabicyclo[3.1.0]hexanes.

3-azabicyclo[3.1.0]hexanes are also valuable to medicinal chemists. For example, compound DOV 21,947 (later named Amitifadine, not shown) bearing a 3-azabicyclo[3.1.0]hexane core reached clinical trials as an antidepressant with a unique therapeutic profile.[63] 3-azabicyclo[3.1.0]hexane-2,4-dione

derivatives proved to be more potent inhibitors of human placental aromatase than their piperidine counterparts.[47]

2.11. 2-azabicyclo[3.3.0]octanes

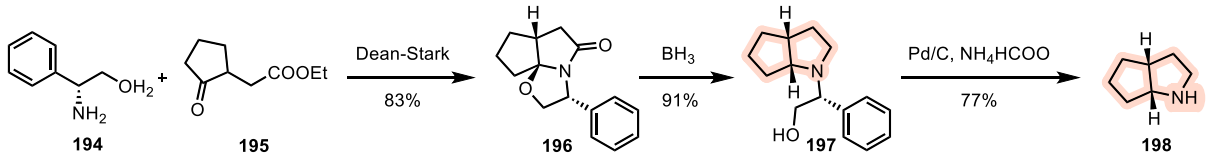
2-azabicyclo[3.3.0]octane with a carboxylic acid functional handle **189** can be synthesized in 3 steps from easily accessible starting materials (Scheme 31).[64] Specifically, triethylamine-mediated alkylation of cyclopentanone-derived enamine **190** with serine-derived chloride **191** gives amino acid **192** in 85% yield. Due to the facile elimination of hydrogen chloride from the former under the reaction conditions, amino acid **192** is obtained in a racemic form. Upon refluxing it in 2 M HCl, amide and ester functionalities are hydrolyzed and a cyclization to imino acid **193** occurs. The latter can be directly isolated after solvent removal. Final reduction with palladium on carbon in the presence of hydrogen furnishes the bicycle **189**, although the yield for this transformation was not reported.



Scheme 31: Teetz's approach towards 2-azabicyclo[3.3.0]octanes.

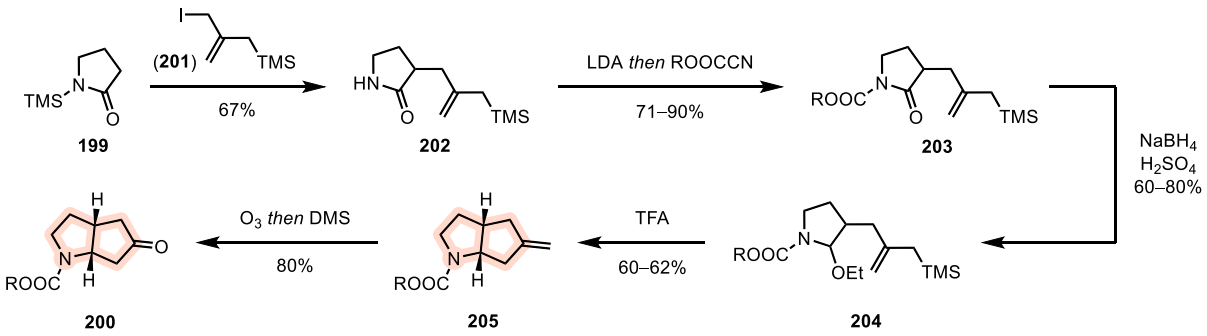
In its enantiopure form, amino acid **189** constitutes an important part of drug Ramipril, which is an ACE inhibitor for managing hypertension.[65]

The 2-azabicyclo[3.3.0]octane scaffold can be synthesized enantioselectively from optically pure phenylglycinol **194** (Scheme 32).[66] Its condensation with ester **195** provides tricyclic lactam **196** in 83% yield. Global reduction with borane gives amino alcohol **197** in 91% yield. Finally, hydrogenolytic conditions employing ammonium formate as a hydrogen source are used to remove the auxiliary to give 2-azabicyclo[3.3.0]octane **198** in 77% yield.



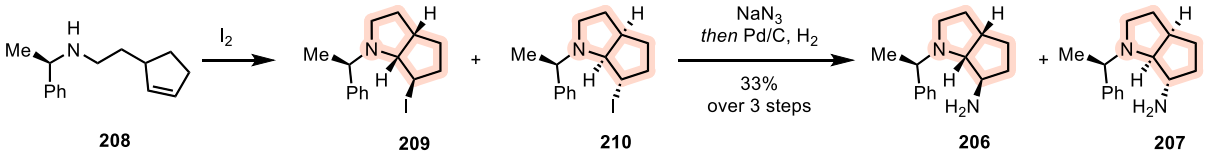
Scheme 32: Ennis' asymmetric approach towards 2-azabicyclo[3.3.0]octanes.

N-protected pyrrolidinone **199** can serve as a suitable starting material for the preparation of 5-oxo-2-azabicyclo[3.3.0]octane **200** (Scheme 33).[67] Deprotonation of the pyrrolidinone with LDA and alkylation with iodide **201** gives, after workup, alkylated pyrrolidinone **202** in 67% yield. The lactam moiety is then protected with either methyl or ethyl cyanoformate, giving protected lactams **203** in 71–90% yields. Reduction with sodium borohydride in ethanol gives allyl silanes **204** in 60–80% yields. Intramolecular Hosomi-Sakurai-type allylation gives penultimate bicyclic carbamates **205** with an exocyclic methylene group, which is ultimately cleaved with ozone to give final products **200** in 48% yield over two steps.



Scheme 33: Remuson's approach towards 2-azabicyclo[3.3.0]octanes.

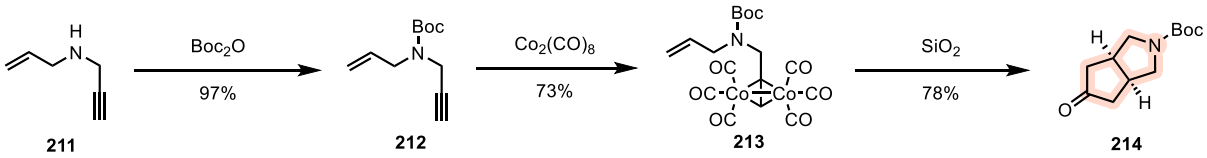
If an amine substituent at C6-positon is desired, 2-azabicyclo[3.3.0]octanes **206** and **207** can be prepared in 3 steps from amine **208** (Scheme 34).[68] Intramolecular iodoamination of endocyclic olefin gives a mixture of diastereoisomeric iodides **209** and **210**, which can be displaced with sodium azide and subsequently separated via column chromatography. Mild hydrogenolysis conditions allow for selective reduction of azides to corresponding amines **206** and **207** without cleaving the benzylic C–N bond.



Scheme 34: Cohen's asymmetric approach towards 2-azabicyclo[3.3.0]octanes.

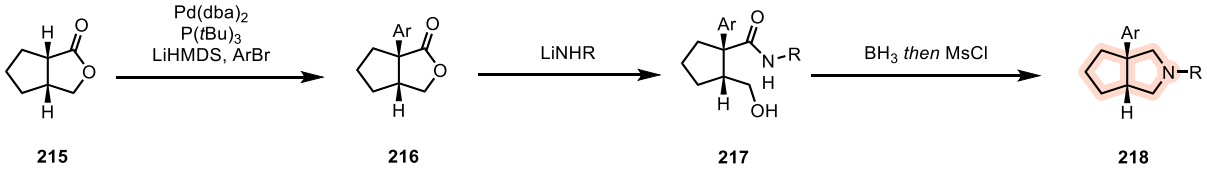
2.12. 3-azabicyclo[3.3.0]octanes

A symmetrical 3-azabicyclo[3.3.0]octane scaffold with a synthetically tractable carbonyl group at the C7-position is synthesized in three steps from allylpropargylamine **211** (Scheme 35).[69] Boc protection gives carbamate **212** in 97% yield. The corresponding hexacarbonyldicobalt complex **213** is isolated via column chromatography after treatment of carbamate **212** with $Co_2(CO)_8$ (73% yield). The complex is then adsorbed on silica and heated in inert atmosphere to effect a reductive Pauson-Khand cyclization and to yield the desired ketone **214**.



Scheme 35: Becker's approach towards 3-azabicyclo[3.3.0]octanes.

3-azabicyclo[3.3.0]octanes arylated at the bridgehead position were prepared from bicyclic lactone **215** in three steps (Scheme 36).[70] The authors described excellent yields for palladium-catalyzed α-arylation, although exact values were not reported. Arylated lactones **216** were then opened with lithium alkyl amides to give the corresponding alcohols **217**. Final borane reduction of the amide moiety and intramolecular *N*-alkylation with MsCl furnished the desired 3-azabicyclo[3.3.0]octanes **218**.

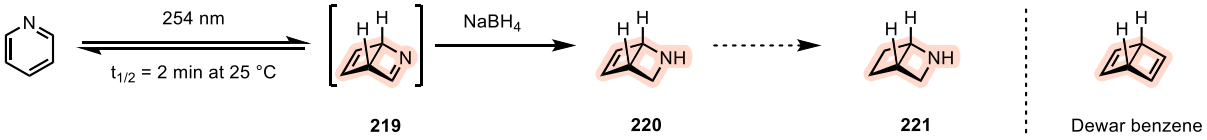


Scheme 36: Shao's approach towards 3-azabicyclo[3.3.0]octanes.

Gliclazide (not shown) is an example of an anti-diabetic medication that features the 3-azabicyclo[3.3.0]octane skeleton.[71]

2.13. 2-azabicyclo[2.2.0]hexanes

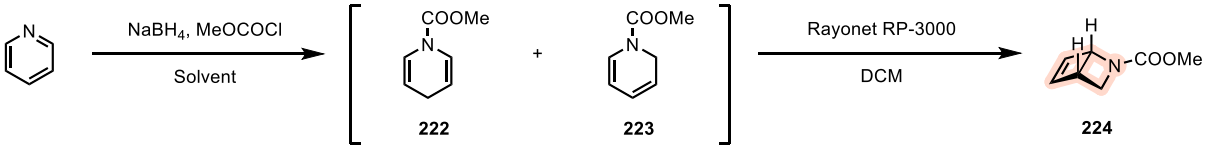
Dewar benzene is a famous valence isomer of benzene (Scheme 37, right). Its nitrogen-containing counterpart, Dewar pyridine (219), was prepared for the first time in 1970 by Wilzbach and Rausch by photoisomerization of pyridine in liquid phase (Scheme 37, left).[72] **219** has a half-life of 2 minutes at 25 °C, meaning that sufficient quantities for NMR analysis could only be prepared by irradiation at reduced temperatures (0 °C). If the irradiation was conducted in aqueous $NaBH_4$ solution, 2H-Dewar pyridine or 2-azabicyclo[2.2.0]hex-5-ene (**220**) was formed.



Scheme 37: Synthesis of Dewar pyridine and its reduction with sodium borohydride.

Further reduction would formally give 4H-Dewar pyridine or 2-azabicyclo[2.2.0]hexane (**221**). 4H-Dewar pyridines will be referred to as 2-azabicyclo[2.2.0]hexanes in the rest of the thesis.

In 1971, Fowler published a procedure for the reductive dearomatization of pyridine in the presence of methyl chloroformate that yielded a mixture of 1,4- (**222**) and 1,2-dihydropyridines (**223**) and indicated the possibility of transforming the 1,2-dihydropyridine **223** into an 2-azabicyclo[2.2.0]hex-5-ene system **224** under photochemical conditions (Scheme 38).[73]

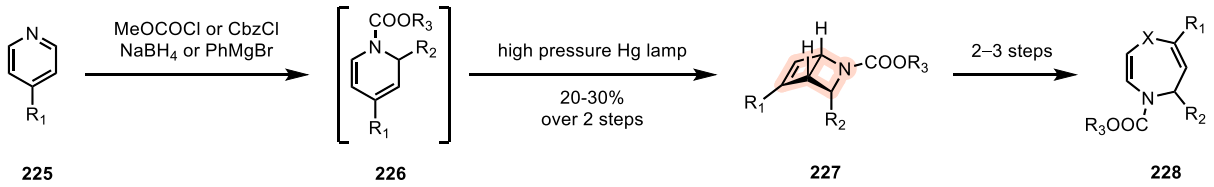


*Scheme 38: Fowler's synthesis and electrocyclization of dihydropyridine **223.***

While dearomatization worked well in various solvents, THF was initially identified as the optimal one. However, if the reaction was run at or below 10 °C, a mixture of 1,2- and 1,4-dihydropyridines (**223** and **222**) was obtained, which could be separated by leveraging the difference in their reactivity towards dienophiles. A significant improvement was made with the discovery that at cryogenic temperatures and with methanol as a solvent, 1,2-dihydropyridine **223** can be obtained almost exclusively (2–4% of 1,4-isomer **222** remained). Although the exact yield was not reported, the experimental setup for preparation of bicyclic structure **224** was disclosed.

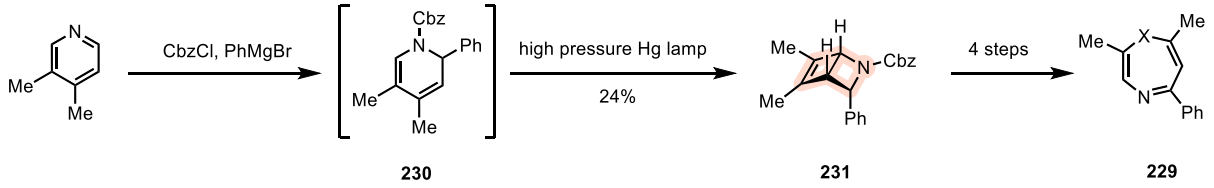
Since the initial discovery, Tsuchiya's group followed up on Fowler's work. 4-substituted pyridines bearing phenyl and methyl substituents **225** were dearomatized with sodium borohydride or phenylmagnesium bromide (Scheme 39).[74] The corresponding 1,2-dihydropyridines **226** were irradiated with a high-pressure mercury lamp to give 2-azabicyclo[2.2.0]hex-5-enes **227** in 20–30%

yields over two steps. However, the authors did not explore these scaffolds as piperidine isosteres but instead used them as intermediates *en route* to azepine derivatives **228** (X = CH_2, O, S, NCOOEt).



Scheme 39: Tsuchiya's expansion of pyridine dearomatization / 4π-electrocyclization scope.

Two years later, the same group published a similar study towards fully unsaturated azepine derivatives **229** (Scheme 40).[75] The authors showed that disubstituted 3,4-lutidine could be dearomatized to give the corresponding 1,2-dihydropyridine **230**, which was, without isolation, exposed to ultraviolet irradiation to give 2-azabicyclo[2.2.0]hex-5-ene **231** in 24% yields over two steps. This was the first example of a trisubstituted 2-azabicyclo[2.2.0]hex-5-ene, although the synthetic utility of methyl substituents is limited.



Scheme 40: First successful dearomatization of a disubstituted pyridine.

Almost 30 years after Fowler's seminal work, two studies were published by Krow et al., in which they utilized state-of-the-art chemical transformations of the time for the preparation of epibatidine analogues based on 2-azabicyclo[2.2.0]hexane system. Epibatidine **232** is a highly potent agonist at nicotinic acetylcholine receptors, making it an appealing candidate for the treatment of neurological disorders. However, it causes considerable side effects like hypertension, neuromuscular paralysis, and seizures. Several epibatidine bioisosteres **233**–**236** were synthesized and evaluated (Figure 9).[76]

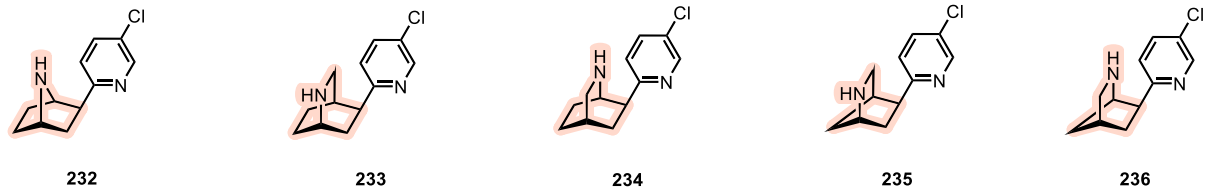
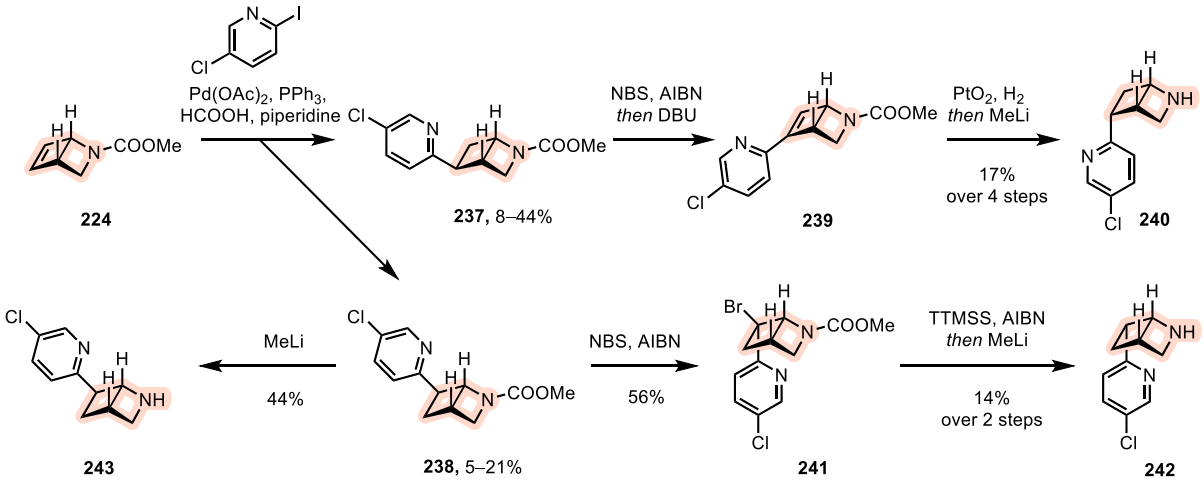


*Figure 9: Structures of epibatidine (**232**) and its isosteres.*

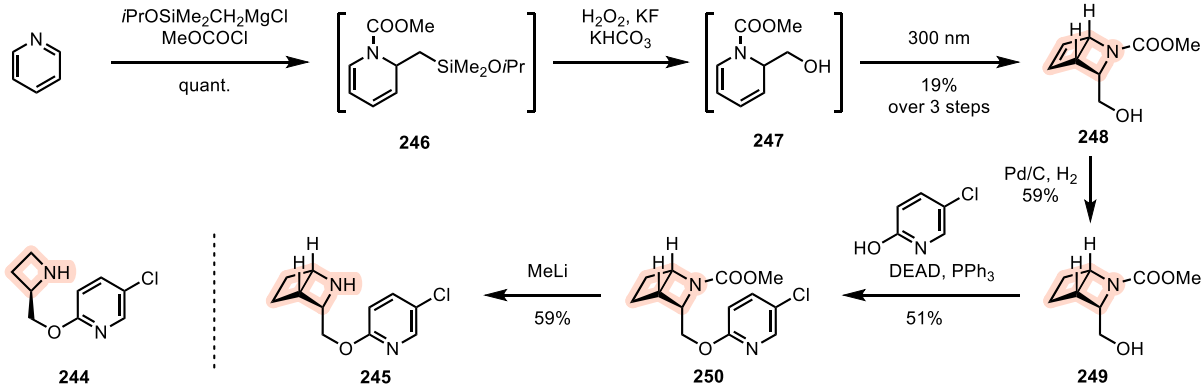
Starting from 2-azabicyclo[2.2.0]hex-5-ene **224**, reductive Heck coupling with 2-chloro-5-iodopyridine gave a separable mixture of 5-*exo* **237** and 6-*exo* **238** isomers in what seemed to be temperature dependent yields (Scheme 41). Stereochemical inversion at the benzylic position was required and both isomers were taken forward separately. 5-*exo*-isomer **237** was brominated under Wohl–Ziegler conditions and then subjected to DBU-mediated elimination to give styrene **239**. Olefin reduction using catalytic amounts of Adams' catalyst and carbamate deprotection with MeLi furnished 5-*endo*-epibatidine bioisostere **240** in 17% yield over 4 steps. Similarly, 6-*exo*-isomer **238** was brominated with NBS and AIBN to give benzylic bromide **241** in 58% yield. Since elimination could not be performed, radical debromination with supersilane was employed. MeLi deprotection then gave 6-*endo*-epibatidine isostere **242** in 14% yield over two steps. Out of two possible *exo*-epibatidine bioisosteres only 6-*exo*-isomer **243** was prepared from **238** by treatment with MeLi in 44% yield. Biological assays

revealed that none of the prepared bioisosteres were as active as epibatidine. This result was rationalized by the lack of a bridged ring structure, which is important for epibatidine's activity.



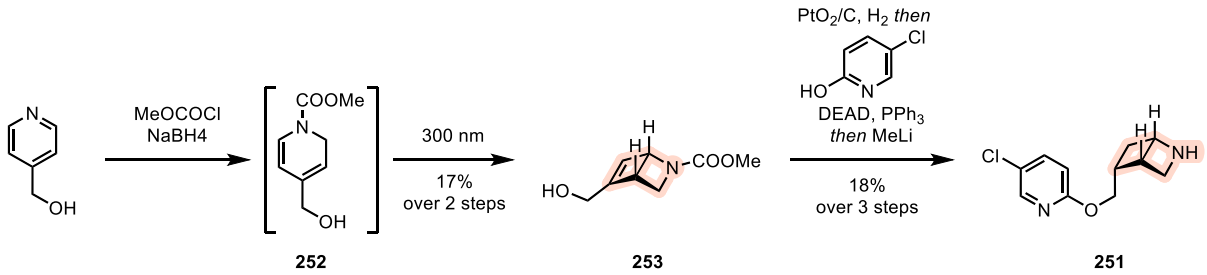
Scheme 41: Krow's synthesis of epibatidine isosteres based on 2-azabicyclo[2.2.0]hexane skeleton.

ABT-594 (**244**) is a nicotinic acetylcholine receptor (nAChR) modulator that was developed in search for epibatidine (**232**) analogues with better therapeutic profiles. As a part of advanced SAR studies, bioisostere **245** was synthesized and its activity was evaluated (Scheme 42).[77] Dearomatization of pyridine with Grignard reagent *i*PrOSiMe$_2$CH$_2$MgCl and methyl chloroformate gave 1,2-dihydropyridine **246** in quantitative yield. The crude **246** was oxidized under Fleming-Tamao conditions to the alcohol **247**, which was then immediately irradiated with ultraviolet light to furnish 2-azabicyclo[2.2.0]hex-5-ene **248** in 19% yield over three steps. Olefin saturation with hydrogen and palladium on carbon yielded saturated alcohol **249**. Mitsunobu etherification with 5-chloro-2-hydroxypyridine yielded ether **250** in 51% yield. Final carbamate deprotection with MeLi gave the desired bicyclic ABT-594 bioisostere **245**.



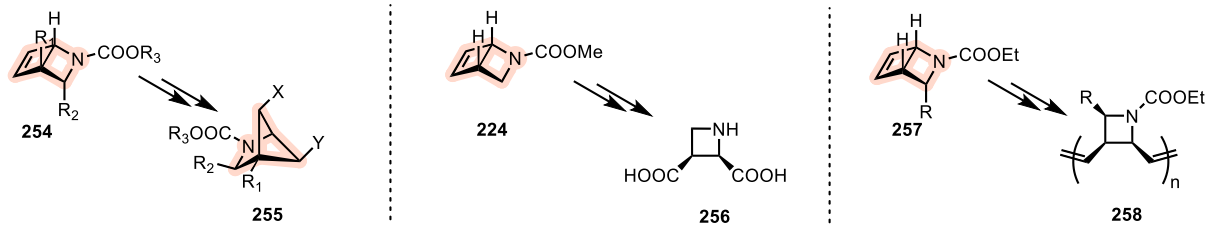
Scheme 42: Krow's synthesis of ABT-594 isosteres.

Its "pseudoaxial" isomer **251** was prepared from 4-(hydroxymethyl)pyridine (Scheme 43). Dearomatization under Fowler's conditions yielded 1,2-dihydropyridine **252** and subsequent photochemical electrocyclization furnished 2-azabicyclo[2.2.0]hex-5-ene **253** with a hydroxymethyl functional handle in 17% yield over two steps. Following the same endgame plan, alcohol **253** was transformed into ABT-594 isostere **251** in a 3-step sequence consisting of catalytic hydrogenation, Mitsunobu etherification and MeLi carbamate deprotection in an overall 18% yield.



Scheme 43: Krow's synthesis of ABT-594 isosteres, continued.

Shifting away from epibatidine bioisosteres, Krow et. al. explored the possibility of transforming 2-azabicyclo[2.2.0]hex-5-ene scaffolds **254** into functionalized 2-azabicyclo[2.1.1]hexanes **255** in a series of publications (Scheme 44, left).[78–84]



Scheme 44: Miscellaneous uses of 2-azabicyclo[2.2.0]hex-5-enes.

Arakawa's group utilized 2-azabicyclo[2.2.0]hex-5-ene **224** to access azetidine-*cis*-2,3-dicarboxylic acid (**256**) in 5 steps (Scheme 44, middle).[85]

A review article highlighting the research of 2-azabicyclo[2.2.0]hex-5-ene chemistry from Krow's, Arakawa's, Tsuchiya's groups, and others was published in 2004.[86] Since then, Nelson's group was interested in ring-opening polymerization of 2-azabicyclo[2.2.0]hex-5-enes **257** to arrive at polyazetidines **258** (Scheme 44, right).[87]

From this brief overview of several existing methodologies for constructing piperidine bioisosteres it is obvious that, in most cases, lengthy syntheses of linear precursors are required. If additional functionality is desired, the whole sequence must be repeated with suitably functionalized precursors, which can significantly impede SAR studies. Catalysis with precious transition metals and reactions with poor atom economy are difficult to avoid. The remaining modular approaches are often plagued with the formation of mixtures of diastereoisomers, which are difficult to separate or give products in higher oxidation states, which must be subsequently adjusted. Hence, the search for malleable piperidine isosteres, which not only overcome these challenges but are also convenient and inexpensive to synthesize and allow for programmable functional group installation, is incomplete. We hypothesized that 2-azabicyclo[2.2.0]hexanes, on the other hand, might offer a solution to these problems. They can be synthesized in 3 steps from commercially available pyridines without relying on precious metal catalysis. However, our literature survey revealed that development and use of this intriguing scaffold remained mainly stagnant since Krow's work 20 years ago. It became obvious to us that its chemistry did not age well with the development of more modern reactions. Therefore, we took it upon ourselves to further gauge the potential of 2-azabicyclo[2.2.0]hexane core and evaluate its suitability for inclusion in SAR studies and related medicinal chemistry campaigns as a potential piperidine bioisostere.

3. 4H-DEWAR PYRIDINES: DEAROMATIVE APPROACH TOWARDS PROGRAMMABLE PIPERIDINE ISOSTERES

3.1. Exit vector analysis (EVA)

We began our work by selecting a handful of the most represented piperidine bioisosters and performing exit vector analysis on their thermodynamically most favorable conformers. Azetidine, pyrrolidine, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane and 2-azaspiro[3.3]heptane were chosen. Given the prevalence of 1,4-disubstituted piperidines in FDA-approved drugs, two exit vectors were placed on each piperidine isostere. The first was placed on the nitrogen atom and the second was placed intuitively on the carbon skeleton so that the overlap with 1,4-disubstituted piperidine would be the greatest. To reduce computational time, methyl groups were selected as the simplest exit vectors. Conformational search followed by energy minimization resulted in the following geometries **A**–**F** (Figure 10).

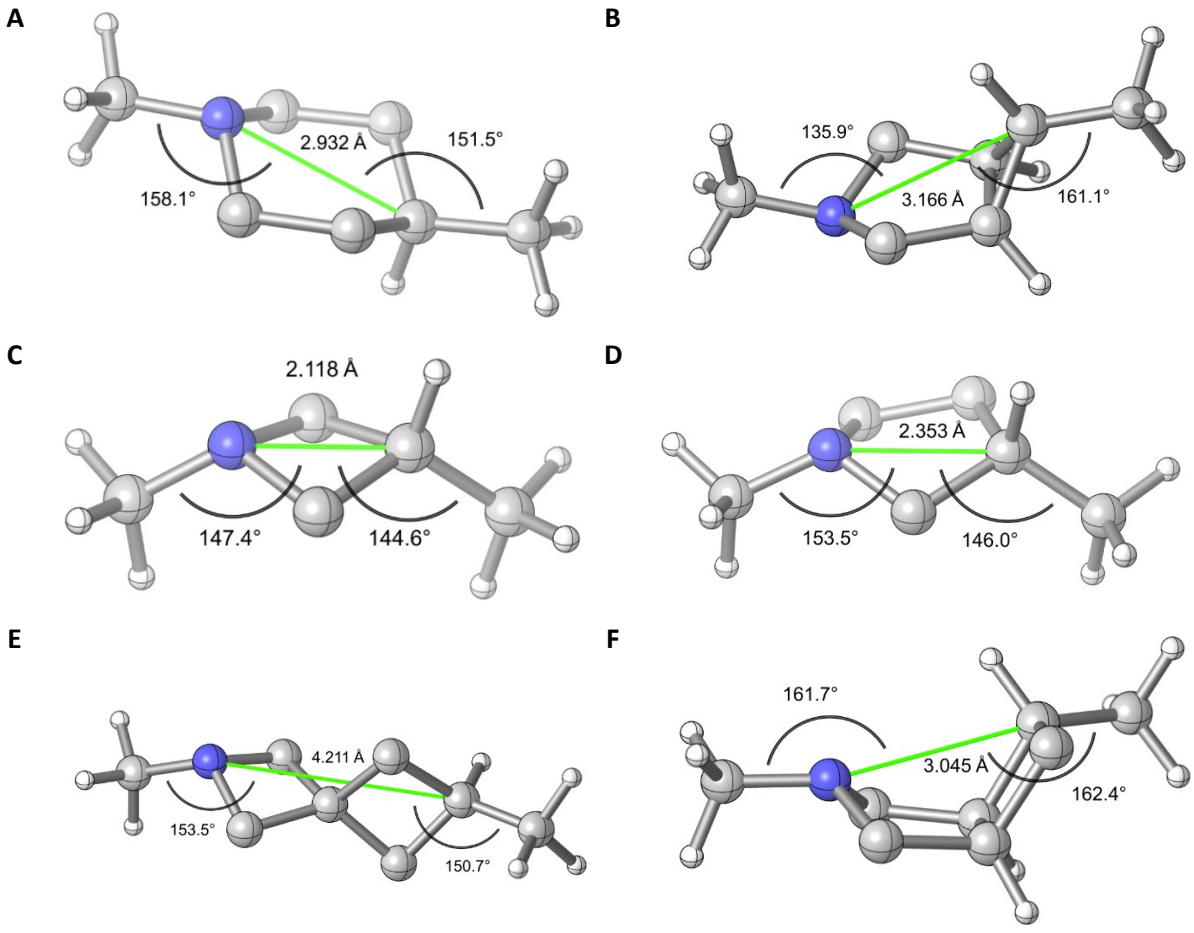


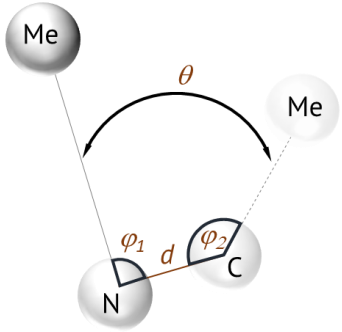
Figure 10: Optimized geometries of 1,2-disubstituted piperidine and its isosteres.

Four parameters were then evaluated (Figure 11):

- Distance between the exit vector bearing nitrogen and carbon atoms d(N–C),
- Dihedral angle θ(Me–N–C–Me),
- Torsional angle ϕ_1(Me–N–C),

- Torsional angle ϕ_2(N–C–Me).

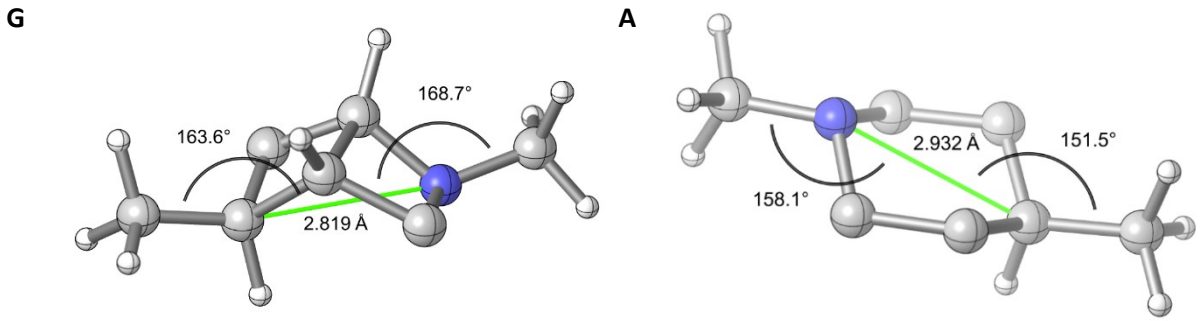
The N–C distance and dihedral angle in 3-azabicyclo[3.1.0]hexane isostere (**B**) match well with the respective values for piperidine (**A**). However, this isostere has a 22° smaller torsional angle ϕ_1 than the reference value. The azetidine isostere (**C**) has the shortest N–C distance (2.1 Å) out of all isosteres evaluated. Additionally, its exit vectors point in opposite ways compared to piperidine **A** ($\Delta\theta$ = 180°). The same conclusion can be made for pyrrolidine isostere **D**, although the N–C distance difference is not as large (Δd = 0.5 Å). 2-azaspiro[3.3]heptane (**E**) can be considered as an elongated piperidine isostere, since its N–C distance is 1.2 Å longer compared to the one found in parent piperidine **A**. Finally, the N–C distance in 3-azabicyclo[3.2.0]heptane isostere **F** matches almost perfectly with the reference value. However, the dihedral angle θ and torsional angle ϕ_2 differ considerably (103° and 11° difference, respectively.)



	d [Å]	θ [°]	ϕ_1 [°]	ϕ_2 [°]
A	2.9	180	158	151
B	3.2	180	136	161
C	2.1	0	147	145
D	2.4	23	154	146
E	4.2	121	153	151
F	3.0	77	162	162

Figure 11: EVA of piperidine and its isosteres.

Next, the same analysis was performed on the "pseudoequatorial" 2-azabicyclo[2.2.0]hexane isostere (**G**) (Figure 12).



	d [Å]	θ [°]	ϕ_1 [°]	ϕ_2 [°]
A	2.9	180	158	151
G	2.8	-56	169	164

*Figure 12: EVA comparison between "pseudoequatorially" substituted 2-azabicyclo[2.2.0]hexane (**G**) and 1,4-disubstituted piperidine with C4-substituent in axial position (**A**).*

It compares very similarly to 3-azabicyclo[3.2.0]heptane isostere **F**. The N–C distance in **G** is about 0.1 Å shorter compared to that of piperidine **A**. Torsional angles ϕ_1 and ϕ_2 are 11° and 13° larger than desired values. Despite the seemingly large difference between dihedral angles ($\Delta\theta$ = 124°), the computed structures of **G** and **A** overlap reasonably well (Figure 13).

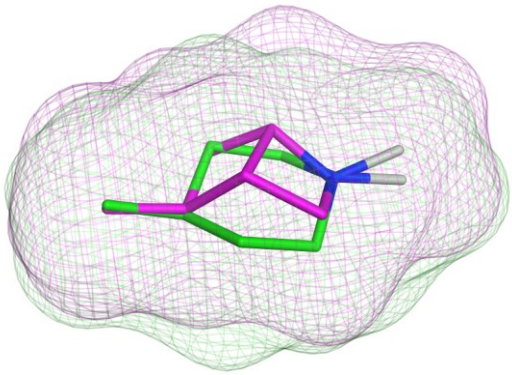
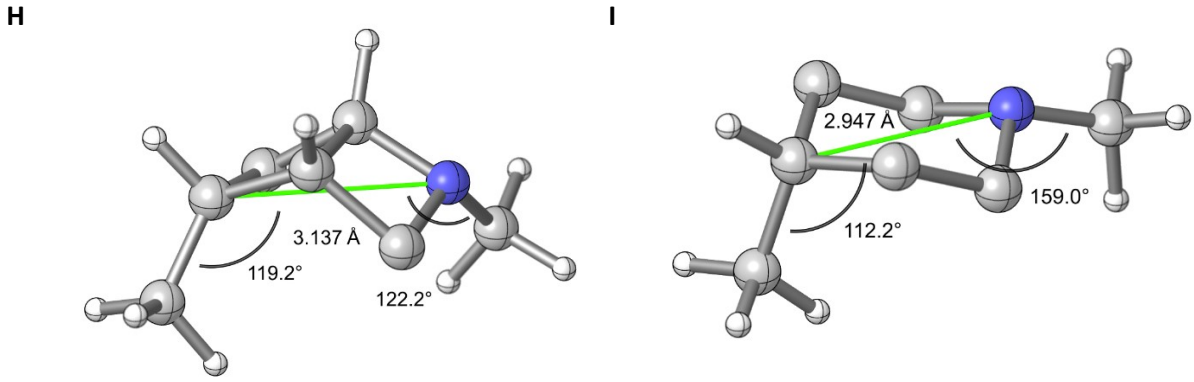


*Figure 13: Structural overlap between computed structures **A** and **G.***

Finally, the EVA was used to compare "pseudoaxial" 2-azabicyclo[2.2.0]hexane (**H**) with its piperidine counterpart, that is, 4-substituted piperidine scaffold with its substituent locked in axial position (**I**) (Figure 14).



	d [Å]	θ [°]	ϕ_1 [°]	ϕ_2 [°]
H	2.9	0	159	112
I	3.1	62	122	119

*Figure 14: EVA comparison between "pseudoaxially" substituted 2-azabicyclo[2.2.0]hexane (**H)** and 1,4-disubstituted piperidine with C4-substituent in axial position (**I).***

With only 0.2 Å longer N–C distance and 7° larger torsional angle ϕ_2, the "pseudoaxial" 2-azabicyclo[2.2.0]hexane (**H**) differs mostly in θ and ϕ_1 values (62° and 37°, respectively). The structural overlap between **H** and **I** was again satisfactory (Figure 15).

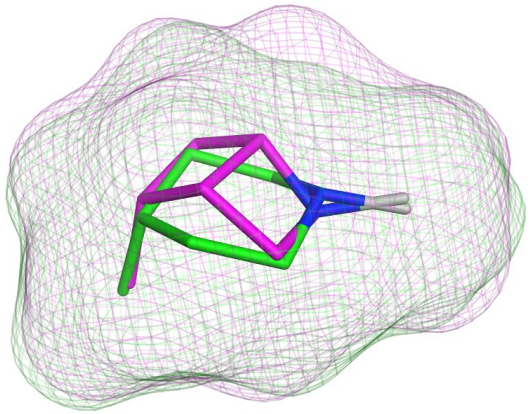


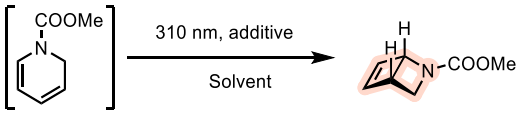
*Figure 15: Structural overlap between computed structures **H** and **I.***

With these results in hand, our focus shifted towards optimizing the electrocyclization step, which is usually the lowest yielding step in the literature and exploring the full substrate scope of 4π-electrocyclization.

3.2. Optimization of 4π-electrocyclization

Literature protocols usually describe photolysis of unpurified 1,2-dihydropyridines in DCM or acetone. Besides setting up a control experiment with 1,2-dihydropyridine **223** in DCM, we screened additional solvents and tried to study the effects of added benzophenone and changing the reaction concentration (Table 2). Yields were determined with ^{1}H NMR analysis of crude reaction mixtures in the presence of 1,3,5-trimethoxybenzene as an internal standard.

*Table 2: **223** 4π-electrocyclization optimization*



223 **224**

Entry	Solvent	Concentration [M]	Additive	224 NMR yield [%]
1	DCM	0.1	–	34
2	DCM	0.2	–	19
3	DCM	0.5	–	n.d.
4	DCM	0.1	10 mol% benzophenone	18
5	Et_2O	0.1	–	36
6	EtOAc	0.1	–	37*
7	MeCN	0.1	–	24*
8	MeOH	0.1	–	10

Reactions performed on 0.2 mmol scale. *Average of 2 runs

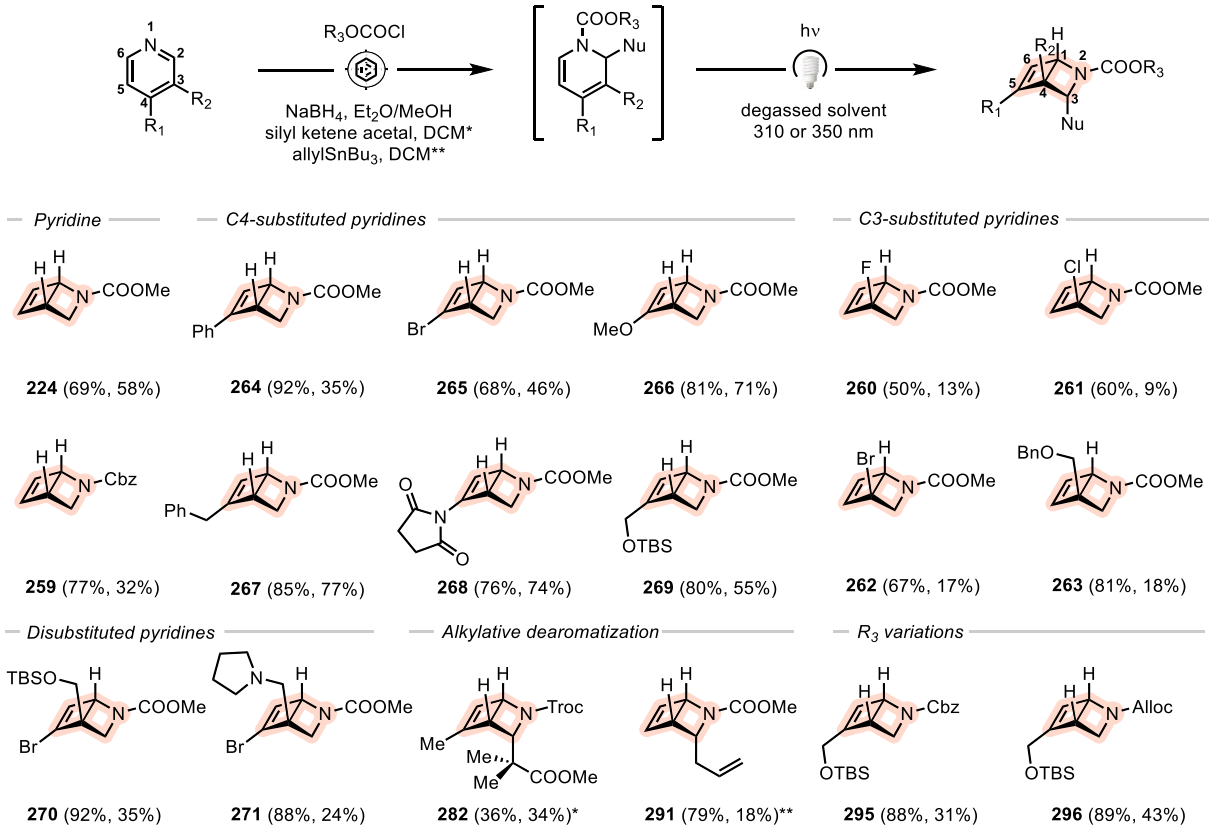
Increasing the reaction concentration had a detrimental effect on the reaction yield (Table 2, entries 1–3) as did the addition of benzophenone (Table 2, entry 4). Diethyl ether and ethyl acetate gave slightly better results than DCM (Table 2, entries 5 and 6). The reaction still occurred in acetonitrile

and methanol, albeit with lower efficiency (Table 2, entries 7 and 8). Side reactivity was observed in methanol as unidentified side products were formed.

From a practical perspective, higher concentrations were employed on larger scales to facilitate material throughput. Even though ethyl acetate seems to be the best solvent for the 4π-electrocyclization, acetone was also used for preparation of 2-azabicyclo[2.2.0]hex-5-enes due to its ability to solubilize decomposition products. While in most cases, both 310 nm and 350 nm wavelength could be used for the 4π-electrocyclization, shorter reaction times could be achieved with 310 nm irradiation. Likewise, reactions performed in borosilicate glassware were slower than their counterparts run in quartz reaction vessels.

3.3. Scope of dearomatization / 4π-electrocyclization sequence

Routine 4π-electrocyclizations of 1,2-dihydropyridine **223** in acetone as a solvent gave the desired product **224** in 19-35% yield range. Replacing acetone with ethyl acetate as the reaction solvent increased the reaction yield to 58%, consistent with the solvent optimization study described above. By using CbzCl instead of MeOCOCl, dearomatization of pyridine proceeded in 77% yield. Subsequent 4π-electrocyclization gave Cbz protected 2-azabicyclo[2.2.0]hex-5-ene **259** in 43% yield (Scheme 45).



Scheme 45: The scope for dearomatization / 4π-electrocyclization sequence.

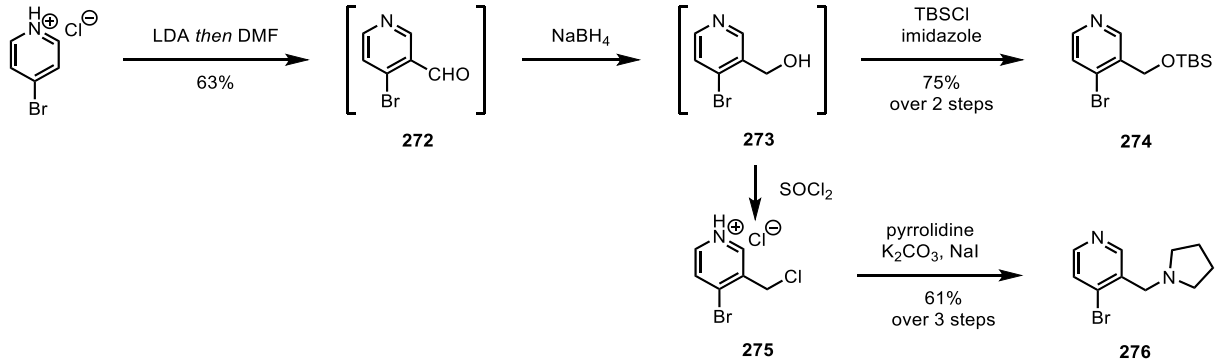
Dearomatization of C2-substituted pyridines was challenging (chapter 3.4). C3-substituted pyridines, on the other hand, successfully underwent dearomatization with $NaBH_4$ and MeOCOCl to give the corresponding 1,2-dihydropyridines, which were immediately subjected to electrocyclization conditions with minimal purification. While dearomatization yields for these substrates were fair to good (50–81%), the subsequent electrocyclization yields were poor (9–18%). C4-substituted 2-azabicyclo[2.2.0]hex-5-enes, bearing fluoro- (**260**), chloro- (**261**), bromo- (**262**) and protected

hydroxymethylene group (**263**) were thus synthesized for the first time. The latter can serve as a precursor to an unnatural amino acid (chapter 5.3).

Dearomatization yields for C4-substituted pyridines were on par with C3-substituted pyridines (68–81%). We were delighted, however, to find that subsequent electrocyclization yields for the former were far superior (35–77%). In this manner, C5-substituted 2-azabicyclo[2.2.0]hex-5-enes, bearing phenyl- (**264**), bromo- (**265**), methoxy- (**266**), phenylmethylene- (**267**), protected amine (**268**) and protected hydroxymethylene group (**269**) were prepared.

2-azabicyclo[2.2.0]hex-5-ene bearing a TBS-protected hydroxymethylene group (**269**) was accessed in 44% yield over two steps from commercially available 4-hydroxymethylpyridine, which presents a 27% increase in yield compared to the intermediate in Krow's synthesis of ABT-594 bioisostere (Scheme 43). Like its constitutional isomer **263**, this substrate can also be transformed into an unnatural amino acid derivative or a diamine linker. The latter can also be synthesized from enimide **268** (chapter 5.3*J*), which itself was prepared in 56% yield over 2 steps.

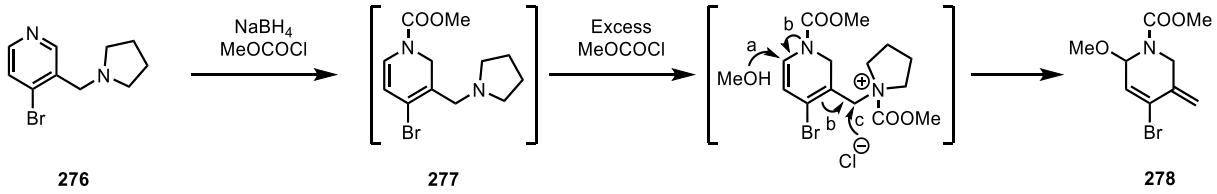
Consistent with the observation from Tsuchiya et al. that disubstituted pyridines are tolerated in the reductive dearomatization / 4π-electrocyclization sequence, disubstituted 2-azabicyclo[2.2.0]hex-5-enes bearing synthetically useful hydroxymethylene **270** and aminomethylene groups **271** were synthesized.[75] The requisite pyridines **274** and **276** were prepared from commercially available starting materials in 3 and 4 steps, respectively (Scheme 46).



*Scheme 46: Synthesis of disubstituted pyridines **274** and **276**.*

Deprotonation and lithiation of commercially available 4-bromopyridinium chloride followed by addition of DMF yielded unstable aldehyde **272** in 63% yield, which was immediately reduced to the significantly more stable benzylic alcohol **273**. The material obtained after reduction step was sufficiently pure to be directly subjected to TBSCl / imidazole protection conditions to give disubstituted pyridine **274** in 75% yield over 2 steps. Alternatively, the subjection of the benzylic alcohol **273** to thionyl chloride afforded benzylic chloride **275** as a hydrochloride salt, which was then used to alkylate pyrrolidine to give tertiary amine **276** in 61% over 3 steps.

While dearomatization of protected (4-bromopyridin-3-yl)methanol **274** was reproducible and uneventful, the dearomatization of 4-bromo-3-(pyrrolidin-1-ylmethyl)pyridine **276** proved to be more challenging. Careful temperature control was required to achieve synthetically useful yields of the desired 1,2-dihydropyridine (**277**) (Scheme 47).

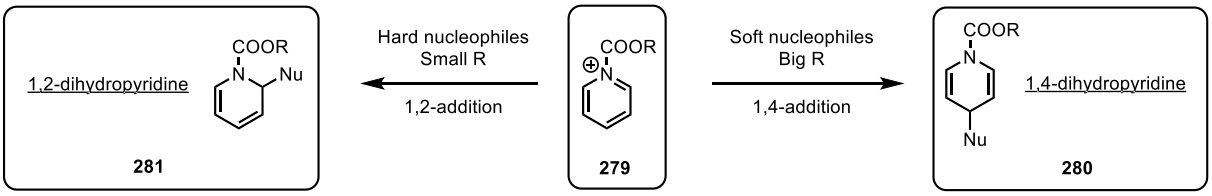


*Scheme 47: Dearomatization of **276** and unexpected side reactivity.*

If the reaction mixture was left at cryogenic temperatures (-78 °C) and was not allowed to warm up, only partial consumption of starting material **276** was observed, regardless of the excess of reagents used. If, however, the reaction was left to warm above -15 °C, the desired reaction product **277** reacted further with excess MeOCOCl and MeOH to give side product **278**. Although the exact mechanism of this transformation was not elucidated, one can envision chloroformate-mediated amine dealkylation followed by direct (paths a and b) or indirect methanol trapping (path c).

Next, with synthetic utility in mind, we explored the scope of nucleophiles that can be used in the dearomatization step instead of $NaBH_4$. We confirmed that products of dearomatization prepared with certain silyl ketene acetals, Grignard reagents and allyltributystannane can undergo subsequent 4π-electrocyclization, giving rise to C3-substituted 2-azabicyclo[2.2.0]hex-5-enes.

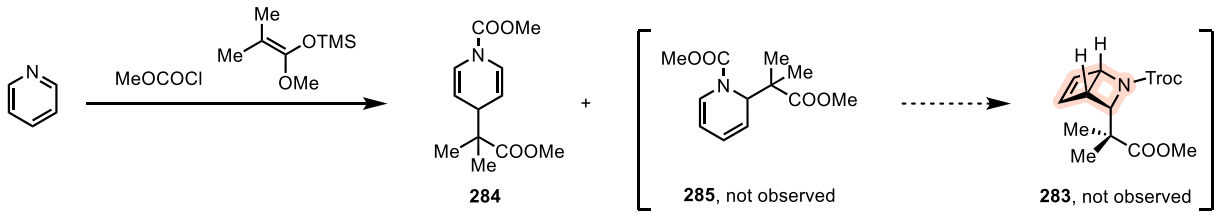
Silyl ketene acetals are soft nucleophiles, which prefer to attack activated pyridinium species **279** in a 1,4-fashion (Scheme 48) to give 1,4-dihydropyridines **280**. Similarly, organozincs and organocuprates prefer 1,4-addition to 1,2-addition. Conversely, Grignard reagents, organotin, and organocadmium compounds give higher selectivity for 1,2-addition and the corresponding 1,2-dihydropyridines **281**. Selectivity of the addition also depends on the size of activating group, with larger R groups favoring 1,4-addition. The reaction solvent selection influences reaction outcome as well.[88]



*Scheme 48: Factors influencing regioselectivity of nucleophilic addition to pyridinium species **279**.*

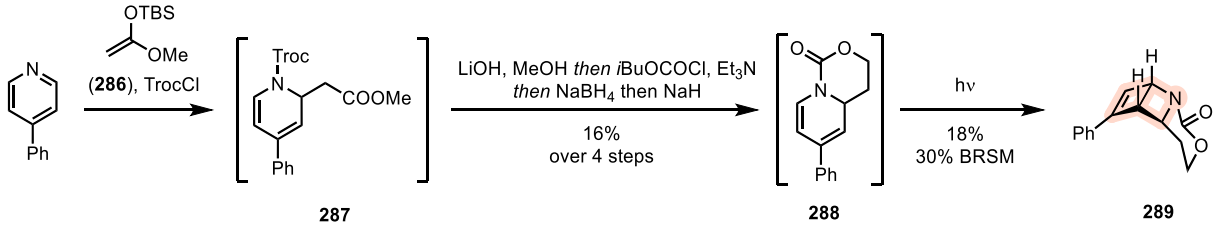
By blocking the C4 position one can achieve C2-selective pyridine dearomatization with soft nucleophiles. Thus, 4-methylpyridine was dearomatized using methyl trimethylsilyl dimethylketene acetal in the presence of Troc-Cl as the activating reagent in 36% yield. 4π-electrocyclization of the crude dihydropyridine could only be performed using 310 nm lamps, and 34% yield of the desired ester **282** was obtained (Scheme 45). Longer wavelengths led to nonspecific decomposition.

Attempts at accessing 2-azabicyclo[2.2.0]hex-5-ene **283** without a methyl group at C5-position by using pyridine instead of 4-methylpyridine were unsuccessful as 1,4-addition (**284**) occurred exclusively. None of the desired 1,2-dihydropyiridne (**285**) was observed, regardless of the solvent and activating group used (DCM, Et_2O/MeOH, MeOH; MeOCOCl) (Scheme 49).



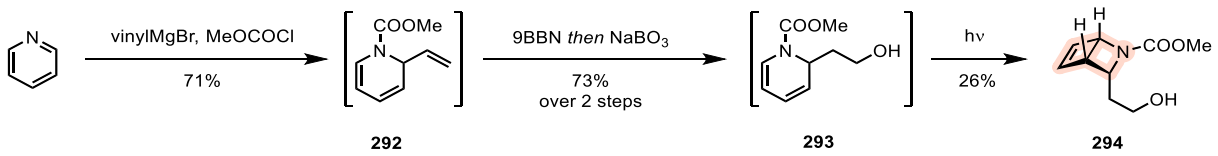
*Scheme 49: Attempts at synthesizing **283.***

Silyl ketene acetal **286** was used to dearomatize 4-phenylpyridine in the presence of Troc-Cl (Scheme 50). 4π-electrocyclization of ester **287** was not successful, presumably due to competing 6π-electrocyclization. We hypothesized that if the ester moiety was reduced, the desired reactivity would be restored and 4π-electrocyclization would become the prevailing pathway. Ester **287** was therefore saponified with LiOH in methanol and the resulting carboxylic acid (not shown) was reduced via the corresponding mixed anhydride with $NaBH_4$. Finally, a cyclization reaction was effected with NaH to give bicycle **288** in 16% yield over 4 steps. Our hypothesis turned out to be correct, as irradiation with 310 nm lamp provided the desired 4-4-6-tricycle **289** in 18% yield (30% BRSM).



*Scheme 50: Synthesis of tricycle **289**.*

Dearomatization of pyridine with allylmagnesium chloride in the presence of MeOCOCl was low yielding (16%). Literature search revealed that allyltributylstannane is a superior nucleophile for this transformation.[89] Thus, we were able to obtain 79% yield of the desired 1,2-dihydropyridine (**290**, not shown), which was then immediately subjected to 310 nm irradiation to give C3 substituted 2-azabicyclo[2.2.0]hex-5-ene (**291**) with a synthetically tractable allyl group, albeit in 18% yield (Scheme 45). Vinyl Grignard reagent performed significantly better than its allylic counterpart and gave 1,2-dihydropyridine **292** in 71% yield (Scheme 51).



Scheme 51: Dearomatization / 4π-electrocyclization sequence with vinylmagnesium bromide as a nucleophile.

To our surprise, however, 1,2-dihydroypridine **292** did not undergo productive 4π-electrocyclization but instead gave us a complex mixture of products (presumably due to 6π electrocyclic ring opening and olefin isomerization. Terminal olefin in **292** was then subjected to oxidative hydroboration with 9BBN and sodium perborate tetrahydrate to give alcohol **293** in 73% yield over 2 steps. By functionalizing the terminal olefin 4π-electrocyclization proceeded as expected and yielded the desired 2-azabicyclo[2.2.0]hex-5-ene **294** in 26% yield (Scheme 51).

The stereochemistry of C3 substituted products was assigned based on similarity to Krow's work in which he and his coauthors explained the complete torquoselectivity (exclusive formation of endo

products) in 1,2-dihydropyridine 4π-electrocyclizations as a consequence of the least nuclear motion pathway principle.[81]

Finally, the protecting group substrate scope was explored. Methyloxycarbonyl group was initially chosen to facilitate substrate purification and characterization. 2-azabicyclo[2.2.0]hex-5-ene products bearing Cbz (**295**), Alloc (**296**) or Troc groups (**297**, not shown) could be prepared as well (Scheme 45). The differences in dearomatization yields are negligible (80-89%; average 86% ± 6%). However, 4π-electrocyclization yields differed considerably with methyloxycarbonyl protected substrate giving the highest yield (**269**, 55%), followed by Alloc- (**296**, 43%), Cbz- (**295**, 31%) and Troc- (**297**, 14%) protected substrates.

A trend became apparent after examining the scope of pyridines that undergo dearomatization and the scope of 1,2-dihydropyridines that undergo olefin 4π-electrocyclization. By only considering substrates with the same nitrogen protecting group (methyloxycarbonyl), the following table of results was obtained (Table 3).

Table 3: 4π-electrocyclization yields based on 1,2-dihydropyridine substitution pattern.

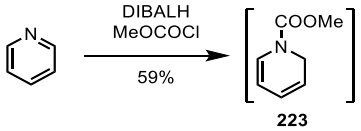
1,2-dihydropyridine substitution pattern	Electrocyclization yield range [%]	Average yield [%]
C2	18–26	22
C3	9–18	14
C4	35–77	60
C3 + C4	24–35	30

4π-electrocyclizations of C4-substituted 1,2-dihydropyridines gave the highest yields, followed by C2- and finally by C3-sustituited 1,2-dihydropyridines. The average 4π-electrocyclization yield of C3, C4-disubstituted 1,2-dihydropyridines lies in between the average yields for C3- and C4-monosubsitituited 1,2-dihydropyridines. The origins of these trends warrant further investigation.

Admittedly, electrocyclization yields for several substrates are poor. This drawback of 2-azabicyclo[2.2.0]hex-5-ene synthesis is ameliorated by the following points:

- there are little practical limitations to dearomatization and electrocyclization scale-ups,
- all starting materials are commercially available and affordable.
- reaction economy is high.
- unique chemical space is accessed in two steps.
- in most cases only one chromatographic purification is needed,
- no precious transition metals are required.

Despite these facts, our goal is to improve electrocyclization yields across the board. We surmise that 1,2-dihydropyridine decomposition is outcompeting the desired electrocyclization. Our hypothesis will be tested by performing the electrocyclization step in a flow chemistry setting. While dearomatization of unsubstituted pyridine with $NaBH_4$ in the presence of MeOCOCl proceeds in 69% yield, the same transformation can be accomplished with commercially available 1 M DIBALH solution in DCM (Scheme 52).



Scheme 52: Dearomatization of pyridine under homogenous conditions.

This ensures the homogeneity of the reaction mixture throughout the process and gives the desired 1,2-dihydropyridine **223** in a comparable 59% yield and almost perfect chemoselectivity (6% of the 1,4-dihydropyridine formed as well). This solution could be hypothetically irradiated in a flow system to streamline the production of **224** even further.

3.4. Limitations

Dearomatization of several examined pyridines failed. Additionally, a few of the synthesized 1,2-dihydropyridines did not undergo productive 4π-electrocyclization. An overview of unsuccessful substrates is shown in the following figure (Figure 16).

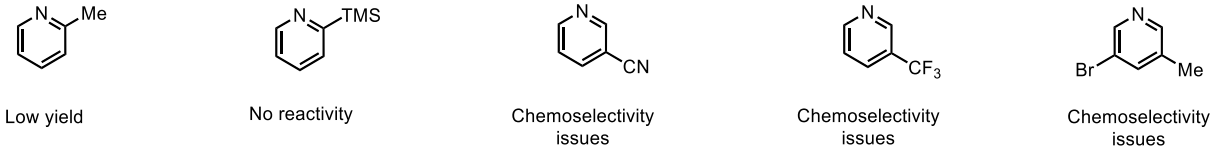
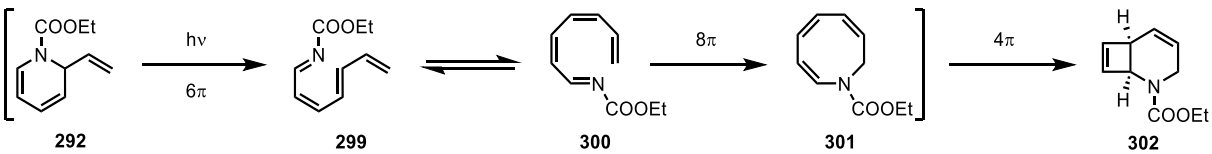


Figure 16: Pyridine dearomatization limitations.

When subjected to dearomatization conditions, C2-substituted pyridines either returned starting material (as in the case of 2-trimethylsilylpyridne) or dearomatization yields were poor (2-picoline; ≤13%), which precluded us from accessing C1-substituted 2-azabicyclo[2.2.0]hex-5-enes directly. C3-substituted pyridines with electron-withdrawing groups like 3-trifluoromethylpyridine or nicotinonitrile suffered from chemoselectivity issues, consistent with findings of Sundberg et al.[90] The same problem was observed for 3-bromo-5-methylpyridine.

As alluded to earlier, 1,2-dihydropyridines bearing a CH_2COOMe or a vinyl group (**287** and **292**) at C2 position gave complex mixtures, presumably due to preferential 6π-electrocyclic ring opening. Not surprisingly, a substrate with a phenyl group at the aforementioned position (**298**) behaved analogously (*vide infra*). All these substrates have an sp^2 hybridized carbon (tautomer form for ester **287**) at the C2-position in common. During the course of our studies, a report corroborating our results was published independently by Williams et al. (Scheme 53).[91] In their case, 1,2-dihydropyridine **292** underwent photochemical 6π-electrocyclic ring opening to give *Z,E*-azatetraene **299**, which isomerized to *Z,Z*-azatetraene **300**. Subsequent 8π-electrocyclization gave dihydroazocine **301**, which underwent 4π-electrocyclization to yield the final product **302**. Their work, however, focused only on 1,2-dihydropyridine **292** and the scope of the aforementioned cascade was not explored.



*Scheme 53: Ring opening of **292** under photochemical conditions by Williams et al.*

A complete list of failed substrates is shown in the next figure (Figure 17). Observation of electrocyclic ring opening with enepivalamide **303** was puzzling, indicating that perhaps only certain types of protecting groups lead to the desired products. Dihydropyridine **304**, derived from pyridine, DMAD

and methyl pyruvate was left unchanged, regardless of the wavelength used (310 nm or 254 nm). Irradiation of nicotinic acid-derived 1,2-dihydropyridines (**305** and **306**) lead to nonspecific degradation products. 1,2-dihydropyridines bearing sp^2 or sp hybridized substituents at the C3-postion (**307** and **308**) were not affected by ultraviolet light as their extended π-system completely shut down reactivity. 4-aminopyridine-derived 1,2-dihydropyridines **309** and **310** gave us a complex mixture and rearomatization, respectively, presumably due to their poor solubility in commonly used organic solvents. These results demonstrate the importance of selecting an appropriate protecting group for the 4-amino substituent for successful product formation (compare with **268**, Scheme 45). Finally, our excitement about the possibility of accessing 1,2-dihydropyridines **311** and **312** bearing synthetically versatile -BPin and medicinally interesting $-CF_3$ groups was short-lived as both electrocyclization attempts were unsuccessful, leading to decomposition and complex mixture of products, respectively.

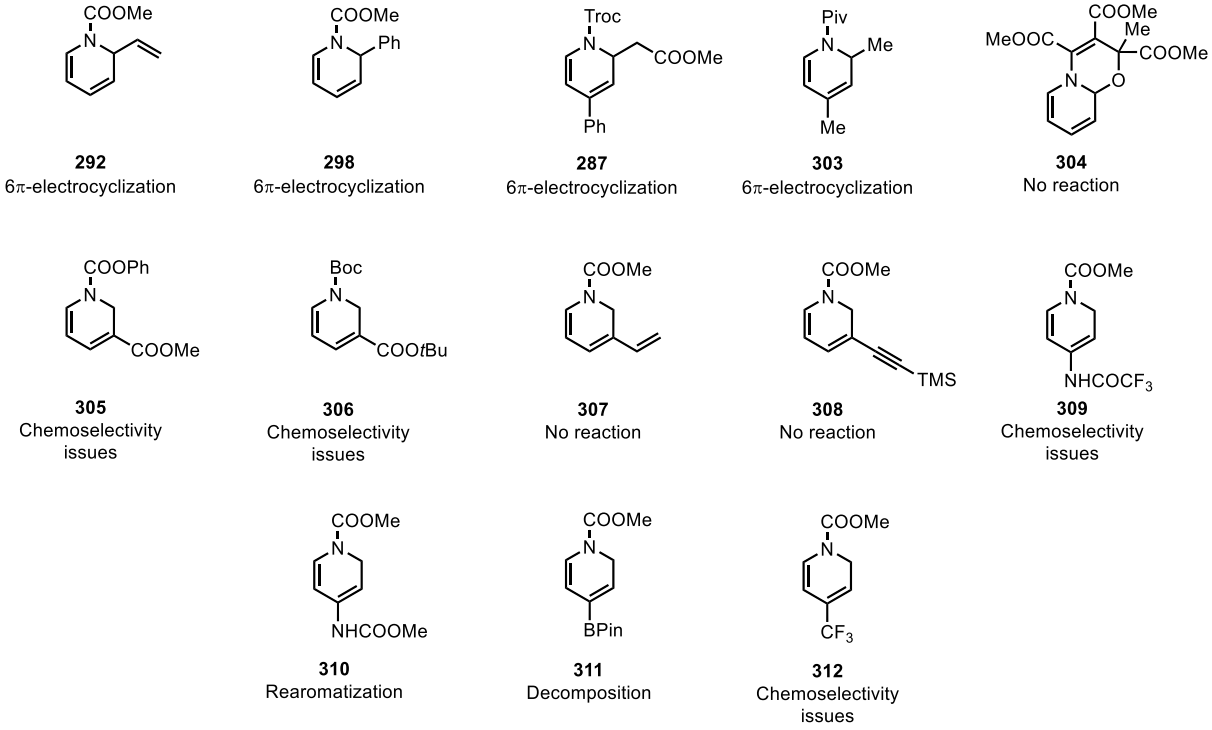
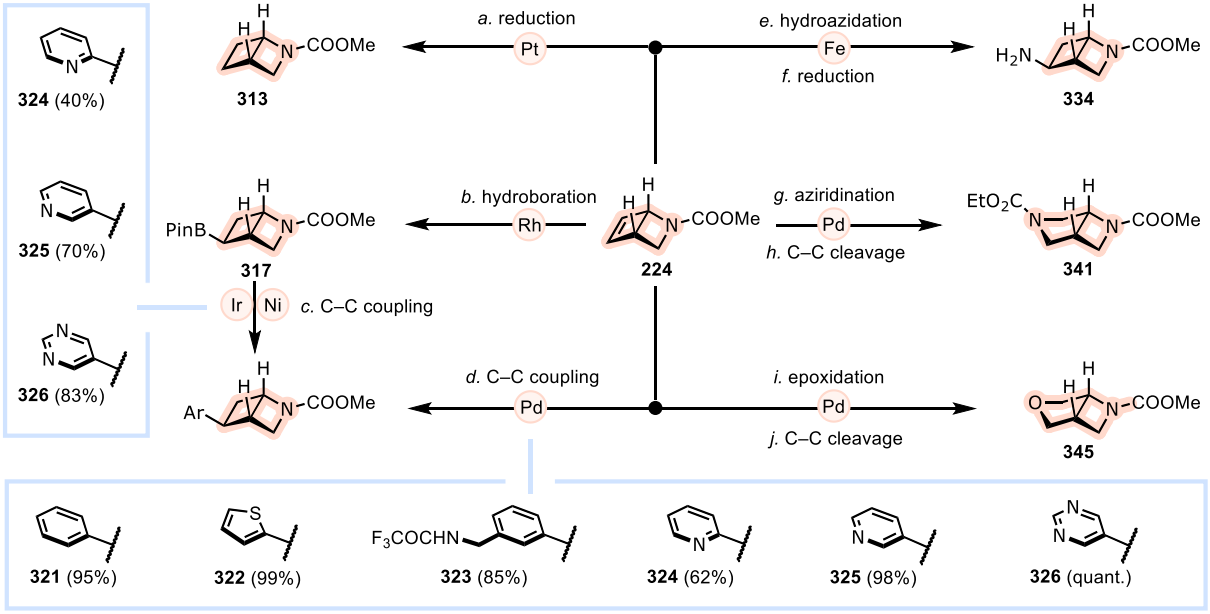


Figure 17: 4π-electrocyclization limitations.

4. OLEFIN FUNCTIONALIZATION AND SKELETAL EDITING

Having explored the scope of substituted pyridines amenable to dearomatization/4π-electrocyclization sequence, we thought of functionalizing 2-azabicyclo[2.2.0]hex-5-enes even further to demonstrate their suitability as piperidine isosteres. To achieve this goal, we wanted to exploit the inherent ring strain of 2-azabicyclo[2.2.0]hex-5-ene scaffold and test more modern olefin functionalization methodologies. A comprehensible but not exhaustive roadmap of olefin functionalization reactions is presented in the following scheme (Scheme 54).



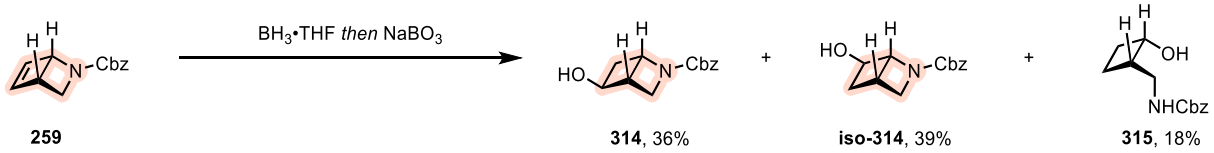
*Scheme 54: Functionalization of **224** and skeletal editing of the 2-azabicyclo[2.2.0]hex-5-ene scaffold (major isomers depicted). (a) 9 mol% PtO_2, 1 atm H_2, MeOH, RT, 1 h, 78%, b) 1.25 mol% $(Rh(COD)Cl)_2$, 2.5 mol% xantphos, 1.2 eq. HBPin, THF, RT, o/n, 92%, r.r. = 1.7 : 1, c) 1.5 eq. morpholine, 5 mol% $Ni(DME)Cl_2$, 1 mol% $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$, 5 mol% dtbbpy, DMF, blue LEDs, RT, 2 h, see experimental section for r.r., d) 5 mol% $Pd(OAc)_2$, 10 mol% xantphos, 2 eq. ArI, 2 eq. HCOOH, 3 eq. piperidine, 30 °C or 50 °C, e) 2 eq. $Fe_2(ox)_3{\cdot}6H_2O$, 6.4 eq. $NaBH_4$, 3 eq. NaN_3, 0 °C, 35 min, 52%, r.r. = 2.0 : 1, f) 18 mol% PtO_2, 1 atm H_2, MeOH, RT, o/n, quant. g) 3 eq. EtOOCNHONs, 21 mol% $BnEt_3NCl$, 6 eq. $NaHCO_3$, DCM/H_2O, 0 °C to RT, 4 h, 44% over 2 cycles, h) 10 mol% Pd/C, 1 atm H_2, MeOH, RT, o/n, 72%, i) 3 eq. "100%" mCPBA, 6 eq. $NaHCO_3$, 0 °C to RT, o/n, 67%, j) 10 mol% Pd/C, 1 atm H_2, MeOH, RT, 2 h, 73%.*

4.1. Hydrogenation

Olefin in **224** could be most conveniently reduced with Adams' catalyst in the presence of hydrogen (1 atmosphere) to yield, after simple filtration, 2-azabicyclo[2.2.0]hexane **313** in 78% yield (Scheme 54).

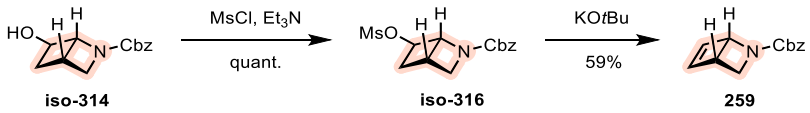
4.2. Hydroboration

If uncatalyzed hydroboration with borane THF complex was performed on olefin **259**, three products were isolated after oxidation with sodium perborate (Scheme 55). Analysis of their 1D and 2D NMR spectra revealed that, besides the expected alcohols **314** and **iso-314**, the third product formed was ring-opened alcohol **315**.



*Scheme 55: Uncatalyzed oxidative hydroboration of **259.***

Since only the more medicinal chemistry-relevant C5-alcohol **314** was desired, this route provided insufficient material throughput. We tried to salvage some of the starting material by recycling the less desired C6-alcohol **iso-314** in two steps (Scheme 56).

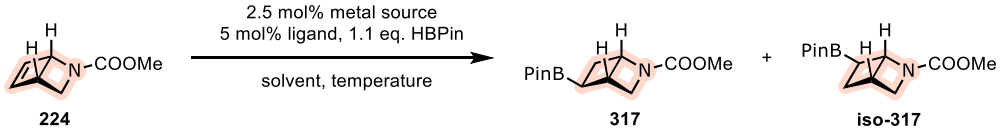


Scheme 56: Recycling of the less desired oxidative hydroboration isomer.

Tosylation was unsuccessful, but under similar reaction conditions mesylation of the secondary alcohol furnished mesylate **iso-316** in quantitative yield. Subsequent elimination was most readily achieved with KO*t*Bu in anhydrous *tert*-butanol as the solvent to give back the olefin **259**. Other elimination conditions and base-solvent combinations like DBU/toluene, KO*t*Bu/DMSO, Tf_2O/DBU, $SOCl_2$, DEAD/PPh_3, and Burgess' reagent gave inferior results.

Still unsatisfied with poor selectivity and laborious recycling of starting material, we explored transition metal-catalyzed hydroboration. Fortunately, no ring opening was observed with rhodium-catalyzed hydroboration, however, this reaction still required some optimization (Table 4). Methyloxycarbonyl protected 2-azabicyclo[2.2.0]hex-5-ene (**224**) was chosen as a model substrate to facilitate reaction mixture analysis. An initial hit was observed with catalytic amounts of Wilkinson's catalyst at room temperature. 38% yield of 1: 1.8 mixture of boronic acid pinacol esters **317** and **iso-317** was obtained (Table 4, entry 1). Subsequently, a small library of mono- and bidentate phosphine ligands was evaluated in combination with $[Rh(COD)Cl]_2$ as the rhodium source (Table 4, entries 2–11). While neither of boronic acid pinacol esters could be obtained selectively, xantphos gave us a 1.7 : 1 mixture, favoring the desired isomer **317** (Table 4, entry 2). DPEphos, on the other hand, gave us a 1 : 2.4 mixture, favoring the less desired isomer **iso-317** (Table 4, entry 7). The use of a cationic rhodium precatalyst, an iridium precatalyst, different solvents, nitrogen protecting groups and reaction temperatures were additionally tested (Table 4, entries 12–23). To our dismay, the constitutional isomer ratio could not be swayed further in either direction.

Table 4: Optimization of transition metal-catalyzed hydroboration



Entry	Temp.	Solvent	Metal source	Ligand	Yield [%]	**317**/iso-**317**
1	RT	THF	$[Rh(PPh_3)_3Cl]$	/	38	1 : 1.8
2	RT	THF	$[Rh(COD)Cl]_2$	xantphos	60	1.7 : 1
3	RT	THF	$[Rh(COD)Cl]_2$	BINAP	45	1.4 : 1
4	RT	THF	$[Rh(COD)Cl]_2$	P(*o*-tol)$_3$	64	1.1 : 1
5	RT	THF	$[Rh(COD)Cl]_2$	dppe	39	1.2 : 1
6	RT	THF	$[Rh(COD)Cl]_2$	dppf	52	1 : 1.7
7	RT	THF	$[Rh(COD)Cl]_2$	DPEphos	63	1 : 2.4
8	RT	THF	$[Rh(COD)Cl]_2$	dppb	51	1 : 1.5
9	RT	THF	$[Rh(COD)Cl]_2$	CyDPEphos	51	1.1 : 1
10	RT	THF	$[Rh(COD)Cl]_2$	sphos	26	1.2 : 1
11	RT	THF	$[Rh(COD)Cl]_2$	CyJohnphos	27	1 : 1.2
12	RT	PhMe	$[Rh(COD)Cl]_2$	xantphos	28	1.6 : 1
13	RT	DCM	$[Rh(COD)Cl]_2$	xantphos	N.R.	N.R.
14	RT	Et_2O	$[Rh(COD)Cl]_2$	xantphos	27	1.9 : 1
15	RT	dioxane	$[Rh(COD)Cl]_2$	xantphos	20	1.5 : 1
16	RT	MeCN	$[Rh(COD)Cl]_2$	xantphos	N.R.	N.R.
17	RT	THF	$[Rh(COD)_2]BF_4$	xantphos	63	1.2 : 1
18	RT	THF	$[Rh(COD)(MeCN)_2]BF_4$	xantphos	69	1 : 1
19	RT	THF	$[Ir(COD)Cl]_2$	xantphos	N.R.	N.R.
20	RT	THF	$[Rh(COD)Cl]_2$	xantphos	33	1.6 : 1**
21	0 °C	THF	$[Rh(COD)Cl]_2$	xantphos	N.D.	1.3 : 1*
22	0 °C	Et_2O	$[Rh(COD)Cl]_2$	xantphos	60	1 : 1*
23	60 °C	THF	$[Rh(COD)Cl]_2$	xantphos	60	1.6 : 1*

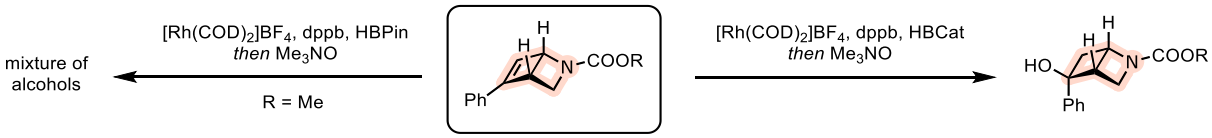
N.R. = no reaction, N.D. = not determined. *Determined with ^{1}H NMR analysis of crude reaction mixture. ** **259** (Cbz) was used instead of **224** (COOMe).

The final improvement of the yield was achieved after realizing the limited stability of boronic acid pinacol esters **317** and **iso-317** towards silica gel column chromatography. By increasing the polarity of mobile phase used and hence by reducing their residence time on the column, boronic acid pinacol esters **317** and **iso-317** were routinely isolated in 78-92% yields.

Cationic rhodium precatalyst $[Rh(COD)_2]BF_4$ in combination with dppb was chosen for hydroboration of styrenyl olefins **264** and **318**. The use of HBpin led to, after oxidation with Me_3NO, a mixture of

alcohols (Table 5). HBCat, on the other hand, gave the desired tertiary alcohols **319** and **320** in 55% yield over 2 steps. These results are in accord with the observation of Crudden et al. that increased steric hindrance of HBPin compared to HBCat results in lower selectivity for branched products of hydroboration.[92]

Table 5: Rhodium catalyzed oxidative hydroboration of styrenyl olefins

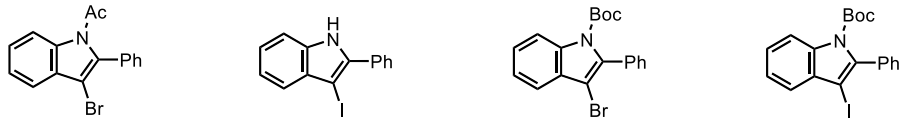


Entry	R	Starting material	Product	Yield [%]
1	Me	**264**	**319**	78
2	*t*Bu	**318**	**320**	55

It is worth noting that rhodium-catalyzed oxidative hydroboration was uniquely suited for our purposes since alternative strategies for accessing **319,** like Mukaiyama hydration and epoxidation/reductive epoxide opening were not successful.

4.3. Hydroarylation

Hydroarylation products could be prepared directly from olefin **224** via reductive Heck reactions. Krow's conditions or Jeffery's conditions were quickly abandoned with the discovery that, by substituting triphenylphosphine with xantphos, higher yields of desired products (**321**–**326**) and their C6 isomers (**iso-321**–**iso-326**) could be obtained reproducibly.[76,93] Besides heteroaryl bromides, aryl iodides could also be employed in the reductive Heck reaction. While reactions with heteroaryl bromides required elevated temperatures (70 °C), aryl iodides reacted at temperatures between 30 and 50 °C. 3-haloindole substrates with different protecting groups (acetyl, free indole, *tert*-butyloxycarbonyl) and leaving groups (Br, I) (**327**–**330**) were not tolerated in this transformation (Figure 18).



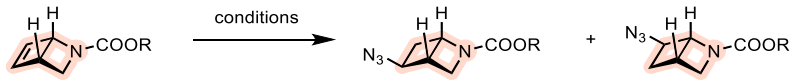
327 **328** **329** **330**

Figure 18: Unsuccessful electrophiles for palladium-catalyzed hydroarlyation

4.4. Hydroazidation

Hydroazidation of olefin **224** could be achieved using two different protocols (Table 6). Xu's conditions gave us 60% yield of azides, favoring the C6-azide **iso-331** (Table 6, entry 1).[94] Slightly lower yield (52%) was obtained with Boger's conditions, but the selectivity was reversed in this case, with the C5-azide **331** forming preferentially (Table 6, entry 2).[95]

Table 6: Hydroazidation of 2-azabicyclo[2.2.0]hex-5-enes.



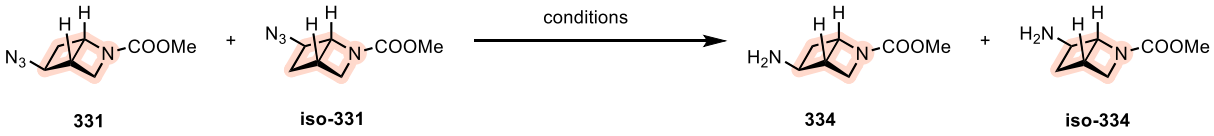
Entry	R	Substrate	Conditions	Yield [%]	Products	C5/C6 ratio
1	Me	**224**	ref. 94	60	**331/iso-331**	1 : 2.1
2	Me	**224**	ref. 95	52	**331/iso-331**	2.0 : 1
3	*t*Bu	**332**	ref. 94	71	**333/iso-333**	*

*Product ratio could not be determined with ^{1}H NMR due to signal overlap.

tert-butyloxycarbonyl protected olefin **332** gave a 71% combined yield of azides **333** and **iso-333**, although their ratio could not be determined with ^{1}H NMR due to signal overlap (Table 6, entry 3).

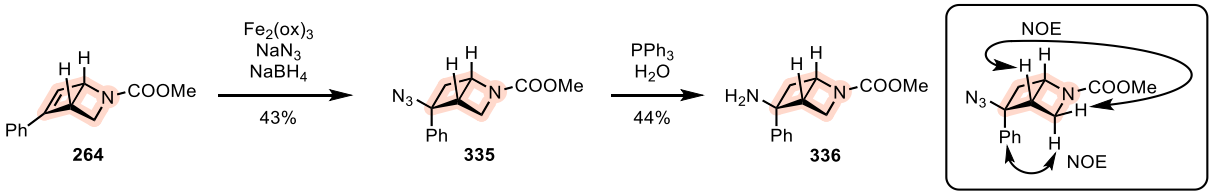
While azides **331** and **iso-331** could not be readily separated using conventional column chromatography, their reduced amine derivatives **334** and **iso-334** could (Table 7). Azide reduction was facile either using Staudinger reduction conditions (Table 7, entry 1) or hydrogenolysis with catalytic amounts of Adams' catalyst (Table 7, entry 2).

Table 7: Reduction of azide mixtures.



Entry	Conditions	Yield [%]
1	PPh_3, H_2O	83
2	PtO_2, H_2	quant.

Xu et al. reported that styrenes are not tolerated under their hydroazidation conditions. Boger's hydroazidation scope, on the other hand, includes styrenyl substrates. The latter protocol allowed us to access a tertiary azide **335** in 43% yield (Scheme 57). Stereochemistry was determined based on NOE analysis.



*Scheme 57: Hydroazidation of styrene **264** and subsequent reduction.*

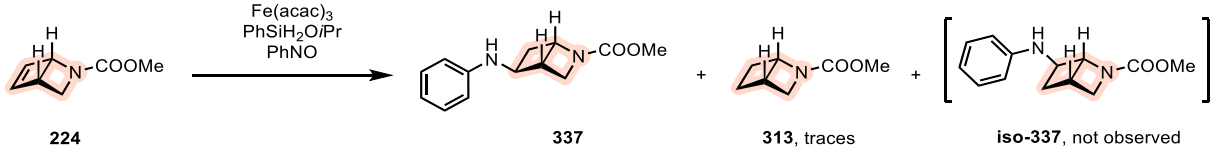
Staudinger reduction of azide **335** was sluggish, but it gave us a serviceable yield of the desired amine **336** (44%).

4.5. Hydroamination

Baran's conditions for olefin hydroamination with nitroarenes were also tested on olefin **224**.[96] We were hoping to establish a more streamlined access to hydroamination products. The unmodified

procedure gave only traces of the desired hydroaminated product **337**. To improve the yield, phenysilane was substituted with Shenvi's silane, because it was shown to give superior hydroamination yields.[97] Additionally, given that nitrosoarenes (formed *in situ*) are postulated to be the actual species that capture alkyl radicals, nitrosobenzene was employed instead of nitrobenzene. Reaction stoichiometry, catalyst loading, concentration and solvent were systematically screened (Table 8). Optimal conditions consisting of limiting olefin **224**, 4.5 equivalents of Shenvi's silane, 2 equivalents of nitrosobenzene, 3 mol% $Fe(acac)_3$ in a 1 : 1 mixture of isopropanol and ethyl acetate at 0.2 M concentration at room temperature yielded 25% yield of C5-constitutional isomer **337** (Table 8, entry 1). C6-isomer **iso-337**, on the other hand, was not observed. Deviating from optimal reaction conditions by performing the reaction under argon (Table 8, entry 2), by using a large excess of nitrosobenzene (Table 8, entry 3), by increasing catalyst loading (Table 8, entry 4), by changing reaction concentration (Table 8, entries 5 and 9), by changing solvent ratio (Table 8, entry 8), by using stoichiometric amounts of nitrosobenzene (Table 8, entry 10) or by replacing ethyl acetate with hexane (Table 8, entry 11) all lead to inferior yields or even arrested product formation. Fluorinated alcohols were shown to give superior yields for MHAT reactions.[98] In our case, however, replacing isopropanol with fluorinated alcohols (Table 8, entries 6 and 7) led to inferior results.

Table 8: Optimization of hydroamination conditions.



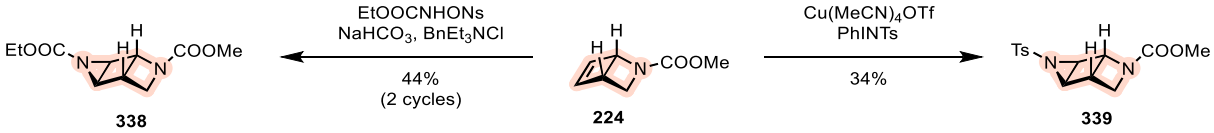
Entry	Olefin [eq.]	Silane [eq.]	PhNO [eq.]	$Fe(acac)_3$ [mol%]	Conc. [M]	Solvent mixture	Yield [%]
1	1	4.5	2	3	0.2	EtOAc/*i*PrOH 1:1	25
2	1	4.5	2	3	0.2	EtOAc/*i*PrOH 1:1	16*
3	1	4.5	5	3	0.2	EtOAc/*i*PrOH 1:1	/
4	1	4.5	2	15	0.2	EtOAc/*i*PrOH 1:1	25
5	3	2	1	5	0.5	EtOAc/*i*PrOH 1:1	Traces
6	1	2	1	5	0.5	EtOAc/TFE 1:1	Traces
7	1	2	1	5	0.5	EtOAc/HFIP 1:1	/
8	1	2	1	5	0.5	EtOAc/*i*PrOH 19:1	Traces
9	1	2	1	5	0.1	EtOAc/*i*PrOH 1:1	Traces
10	1	4	1	5	0.5	EtOAc/*i*PrOH 1:1	17
11	1	2	1	5	0.5	hexane/*i*PrOH 1:1	12

* Reaction conducted under argon atmosphere

4.6. Aziridination

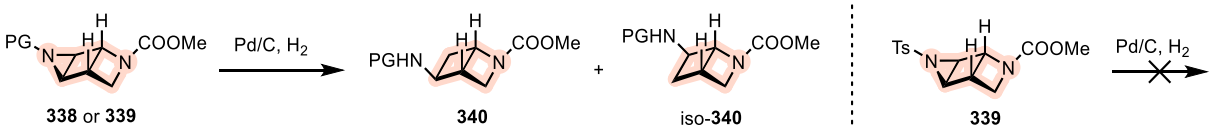
Aziridination was the most challenging transformation as literature conditions furnished only 35% yield of the 3-4-4 tricycle **338** along with 54% yield of recovered starting material **224** (Scheme 58, left). Resubjecting the recovered starting material to the same conditions furnished, after pooling material together, 44% yield of the desired product **338**. Triethylamine as a homogenous base was

completely ineffective in this case. Kürti's aziridination was also attempted without success.[99] Evans' conditions with catalytic amounts of $Cu(MeCN)_4OTf$ and stoichiometric amounts of PhINTs allowed us to access the desired tricycle **339** with a different nitrogen protecting group, albeit in 34% yield (Scheme 58, right).[100]



Scheme 58: Aziridination attempts.

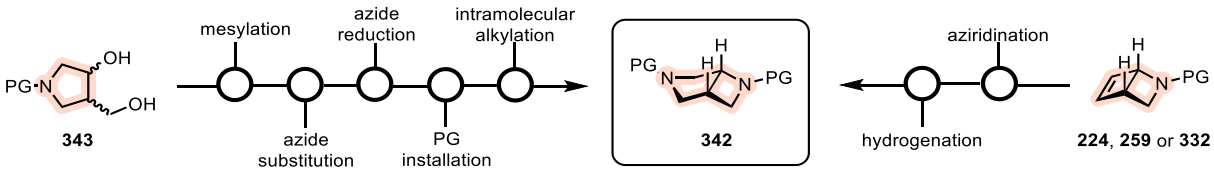
With tricycles **338** and **339** in hand, we wanted to explore the possibility of reductive aziridine opening, which would hypothetically lead to protected amines **340** and **iso-340** (Scheme 59).



Scheme 59: Attempts at reductive aziridine opening.

To our surprise, catalytic hydrogenation of **338** yielded bicycle **341** in 72% yield (Scheme 54), as a result of the cleavage of C5–C6 carbon–carbon bond instead. The nitrogen protecting group plays an important role as sulfonamide **339** was left unreacted under identical hydrogenation conditions (Scheme 59, right).

We were intrigued by the structure of bicycle **341**, which could serve as an elongated piperazine isostere. The literature search revealed that protected 3,6-diazabicyclo[3.2.0]heptanes (**342**) can be accessed from a mixture of protected diols **343** through a series of reactions consisting of double alcohol mesylation, substitution of a primary mesylate with an azide nucleophile, azide reduction, protection of the resulting primary amine and final intramolecular alkylation (Scheme 60, left).[101] Starting with protected 2-azabicyclo[2.2.0]hex-5-enes **224**, **259** or **332**, aziridination and hydrogenation would give the same product in only 2 steps (Scheme 60, right).

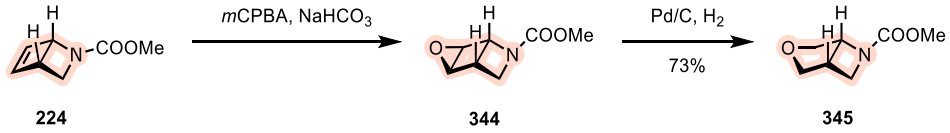


*Scheme 60: Comparison of two routes towards potential piperazine isosteres **342**.*

4.7. Epoxidation

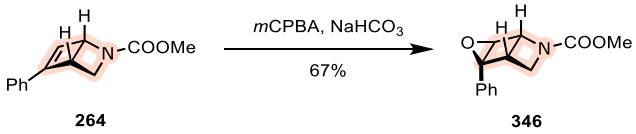
The next logical step was to test the serendipitously discovered reaction on the corresponding epoxide **344** to get to the morpholine isostere **345** (Table 9). *m*CPBA epoxidation was sluggish despite the large excess used. By purifying commercially available *m*CPBA according to the procedure from Aggarwal et al.[102] we were able to achieve full consumption of starting material and 64% yield of the desired epoxide **344**. Gratifyingly, exposure of the epoxide **344** to catalytic hydrogenation conditions yielded the desired 3-oxa-6-azabicyclo[3.2.0]heptane scaffold **345** in 73% yield.

*Table 9: Epoxidation of **224** and reductive epoxide opening.*



*m*CBPA quality	Outcome / **344** Yield [%]
Commercial (≈ 75%)	Starting material : product = 1 : 2.6
Purified (≈ 100%)	Full consumption of starting material; 64%

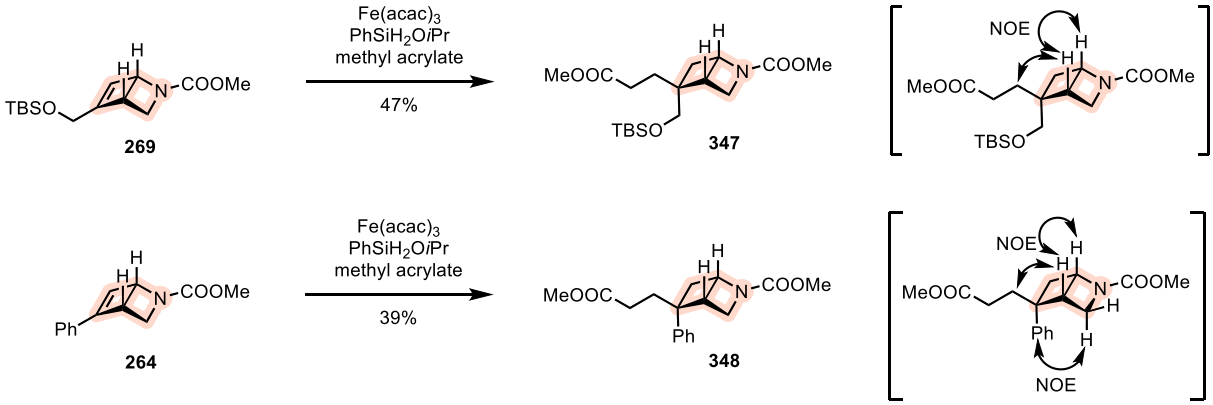
Purified *m*CPBA could also be used to epoxidize C5-substituted 2-azabicyclo[2.2.0]hex-5-ene **264** to give epoxide **346** in 67% yield (Scheme 61).



*Scheme 61: Epoxidation of styrene **264**.*

4.8. Reductive olefin coupling

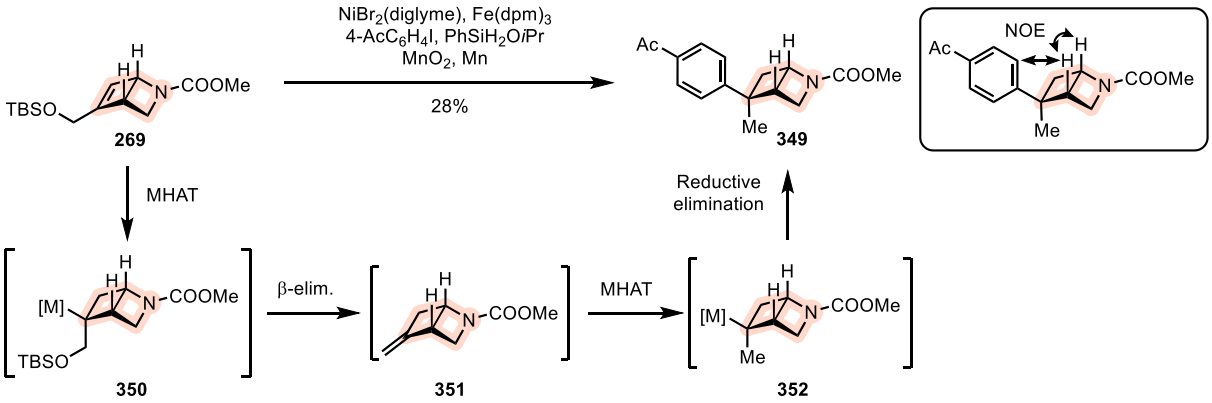
Hydrofunctionalization reactions were also tested on C5-substituted 2-azabicyclo[2.2.0]hex-5-enes. In order to obtain a quaternary carbon atom at C5, Baran's reductive olefin coupling with Shenvi's silane and methyl acrylate was employed (Scheme 62).[97,103] 2-azabicyclo[2.2.0]hex-5-ene with protected hydroxymethylene group at C5-position **269** gave the desired ester **347** in 47% yield at room temperature. Reductive olefin coupling of styrenyl olefin **264** was more challenging. The combination of stoichiometric amounts of $Fe(acac)_3$, superstoichiometric amounts of methyl acrylate and Shenvi's silane at elevated temperature was required to obtain 39% yield of the desired product **348**. In both cases, NOE analysis revealed that the coupling occurred on the convex face of the 2-azabicyclo[2.2.0]hex-5-ene scaffold.



*Scheme 62: Reductive olefin coupling between tertiary olefins **269** and **264** and methyl acrylate.*

As the aryl group ended up on the concave face of the 2-azabicyclo[2.2.0]hexane scaffold with reductive olefin coupling protocol (as in **348**), we envisioned that by employing Shenvi's hydroarylation protocol for accessing quaternary stereocenters we could prepare 2-azabicyclo[2.2.0]hexane bearing a quaternary carbon atom at C5 position and with the aryl group on the convex face (Scheme 63).[104] Upon exposure of **269** to $NiBr_2$(diglyme), $Fe(dpm)_3$, manganese,

manganese dioxide, Shenvi's silane and 4-iodoacetophenone, hydroarylated product **349** could be obtained in 28% yield. While the NOE correlation analysis suggests that the aryl group is on the convex face of the bicycle, an unexpected reduction occurred as well. We propose that after the first MHAT, species **350** undergoes β-elimination to yield olefin **351**. The second MHAT would then give species **352**, which is arylated to give the final product **349**.



Scheme 63: Dual nickel/iron catalyzed hydroarylation attempts.

5. FUNCTIONAL HANDLE INTRODUCTION AND C–C/C–X COUPLINGS

Having explored a variety of olefin (hydro)functionalization reactions, our focus shifted towards functional group interconversions and C–C/C–X couplings. Given the accessibility of 2-azabicyclo[2.2.0]hex-5-ene scaffold, we sought to demonstrate that there were numerous synthetic advantages which our approach afforded. Between the readily tunable oxidation states available and the variety of functional handles we could access, we sought to demonstrate the seamless incorporation of this scaffold into drugs and drug candidates as piperidine isosteres.

5.1. Dual photo/nickel catalysis for C(sp^2)–C(sp^3) coupling

By employing conditions for C(sp^2)–C(sp^3) coupling reactions between boronic acid pinacol esters and aryl halides from Maier et al., we were able to transform the mixture of hydroboration products **317** and **iso-317** into products of formal hydroarylation **324**–**326** (Scheme 54).[105] Irradiation of DMF solutions of $NiCl_2$(diglyme), dtbbpy, Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6, morpholine, aryl bromides and boronic acid pinacol esters **317** and **iso-317** with blue LEDs gave us hydrorylation products (**324**, **325** and **326** as mixtures with their constitutional isosteres **iso-324**, **iso-325** and **iso-326**) in 40–83% yields. However, in contrast to the original report, only selected electron-deficient heteroaryl bromides could be used in our case. A list of unsuccessful coupling partners is shown in Figure 19.

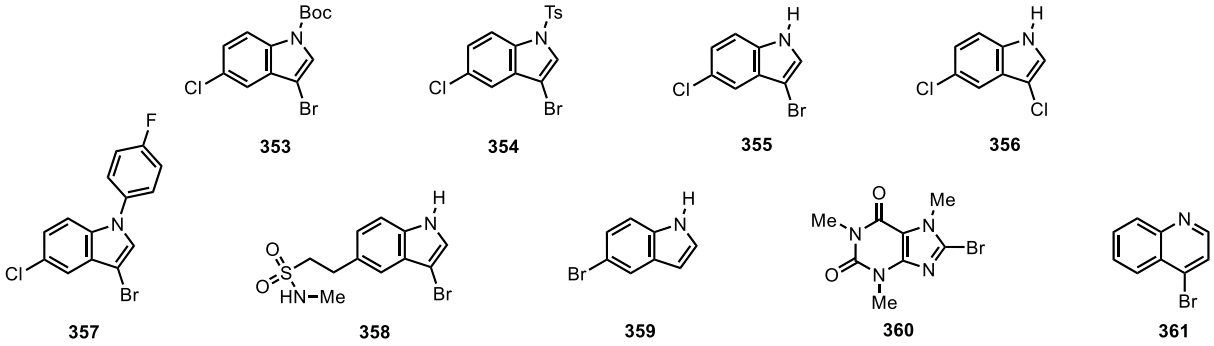


Figure 19: List of unsuccessful coupling partners for dual photo/nickel catalyzed cross-coupling.

The list includes indoles with different protecting groups (*tert*-butyloxycarbonyl (**353**), tosyl (**354**) and aryl (**357**)), free indoles with different leaving groups (bromide (**355**), chloride (**356**)), a sulfonamide (**358**), 5-bromoindole (**359**), caffeine derivative (**360**) and 4-bromoquinoline (**361**). The major side reactivity channel in these cases was unproductive protodebromination, regardless of catalyst loading, reaction concentration, and irradiation time.

A comparison between palladium-catalyzed hydroarylation and dual photo/nickel catalyzed cross-coupling is showcased in the following table (Table 10).

Table 10: Comparison of reductive Heck and dual photo/nickel catalyzed cross-coupling for synthesis of hydroarylated 2-azabicyclo[2.2.0]hexanes.

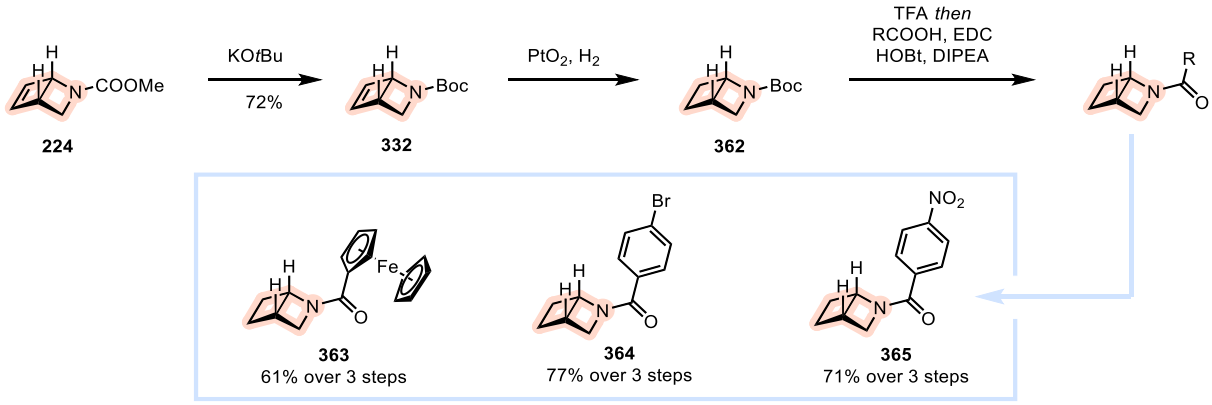
		Ni/Ir cat. cross-coupling		Pd cat. hydroarlyation	
Entry	Products	Yield [%]	Ratio	Yield [%]	Ratio
1	**324**, **iso-324**	40	*	62	*
2	**325**, **iso-325**	70	1.8 : 1	98	1 : 1
3	**326**, **iso-326**	83	1.1 : 1	quant.	1 : 1

*Ratio could not be determined due to NMR signal overlap

Neither of the two methods allowed us to use halogenated indoles as electrophilic coupling partners. While palladium-catalyzed hydroarylation generally gave higher yields and proceeded directly from olefin **224**, a mixture of boronic acid pinacol esters **317** and **iso-317** had to be isolated before photo/nickel coupling, adding an extra step to the overall sequence.

5.2. Deprotections and amide bond formation

In 2014, amide bond formation was the most frequently employed reaction in medicinal chemistry.[106] We wanted to demonstrate that 2-azabicyclo[2.2.0]hexanes and 2-azabicyclo[2.2.0]hex-5-enes are competent partners in amide bond formation reactions. To this end, *tert*-butyloxycarbonyl protected 2-azabicyclo[2.2.0]hexane (**362**) was prepared in two steps (Scheme 64).



Scheme 64: Carbamate protecting group exchange, deprotection and amide bond formation.

First, methoxycarbonyl protecting group in **224** was exchanged with *tert*-butyloxycarbonyl protecting group in **332** with potassium *tert*-butoxide in anhydrous THF in 72% yield. Subsequent hydrogenation in the presence of Adams' catalyst gave saturated derivative **362**, which was deprotected with TFA. Finally, EDC-mediated amide coupling with different carboxylic acids furnished amides **363**–**365** in 61–77% yields over three steps. Atom connectivity in **363** was confirmed via an X-ray analysis of a single crystal (Figure 20).

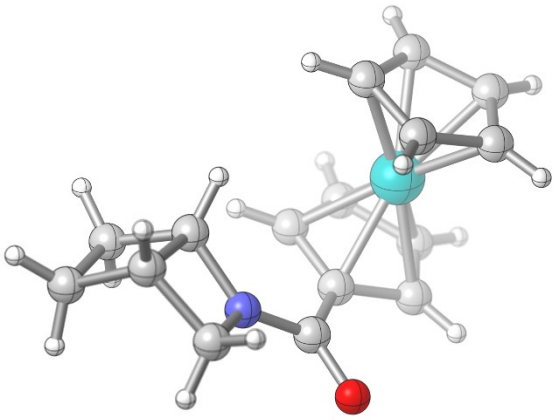
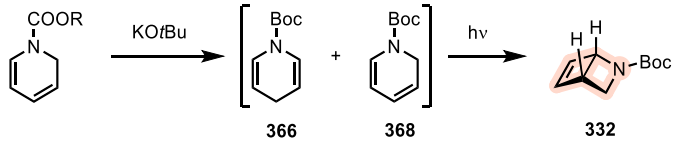


*Figure 20: Crystal structure of **363**.*

In the Journal of Medicinal Chemistry in 2014, *tert*-butyloxycarbonyl protecting group installation and removal were the third most frequent transformations reported.[106] Together with the ease of its removal from the 2-azabicyclo[2.2.0]hexane scaffold, we explored the possibility of introducing this protecting group before the 4π-electrocyclization step and directly accessing valuable building block **332**. However, *tert*-butyl chloroformate is unstable at room temperature and needs to be prepared from toxic phosgene immediately before use. Unaware of reports from Sundberg et al., protecting group exchange was attempted on methyloxycarbonyl protected 1,2-dihydropyridine **223** using potassium *tert*-butoxide at room temperature (Table 11).[107]

Table 11: Identification of suitable conditions for 1,2-dihydropyridine carbamate protecting group exchange.

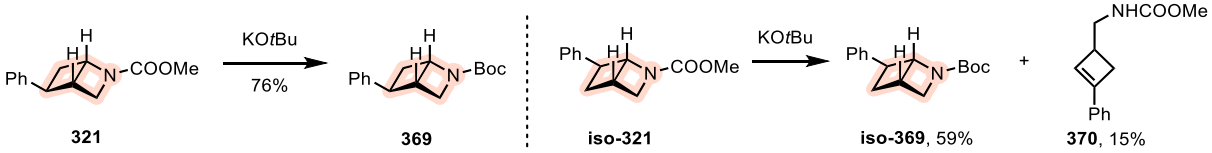


366 **368** **332**

Entry	R	Substrate	Temperature	Result
1	Me	**223**	RT	67% of **366**
2	Me	**223**	-78 °C ⟶ -30 °C	mixture
3	Ph	**367**	-78 °C	96% of **368**

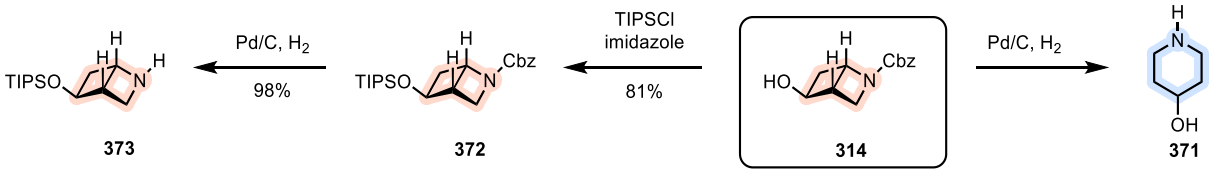
Under these conditions (Table 11, entry 1), protecting group exchange was complete, however 1,2-dihydropyridine isomerized to 1,4-dihydropyridine completely to yield **366** in 67% yield. The reaction was repeated at cryogenic temperatures (Table 11, entry 2). Monitoring the reaction at various temperatures between -78 °C and -30 °C revealed that protecting group exchange and olefin isomerization occur at similar rates. Thus, a mixture of products was isolated. Ultimately, we decided to prepare phenyloxycarbonyl protected 1,2-dihydropyridine **367** according to the literature procedure.[108] Protecting group exchange with this substrate occurred readily at -78 °C. At this temperature, the rate of olefin isomerization was negligible and the desired *tert*-butyloxycarbonyl protected 1,2-dihydropyridine **368** was obtained in 96% yield (Table 11, entry 3). Subsequent 4π-electrocyclization was uneventful, yielding the *tert*-butyloxycarbonyl protected 2-azabicyclo[2.2.0]hex-5-ene **332** in 29% yield.

For the majority of substrates in this study, the transformation of the methyloxycarbonyl protecting group into *tert*-butyloxycarbonyl protecting group with potassium *tert*-butoxide prior to amide bond formation provided higher overall yields, due to the subsequent TFA deprotection having much cleaner reaction profile. Substrates like **321** were cleanly transformed into the corresponding Boc-derivatives (*e.g.* **369)**, however, substrates like **iso-321** displayed nonnegligible side reactivity (Scheme 65). Besides isolating 59% yield of the desired *tert*-butyloxycarbonyl protected product **iso-369**, cyclobutene **370** was also isolated in 15% yield.



Scheme 65: Unexpected side product formation upon carbamate protecting group exchange.

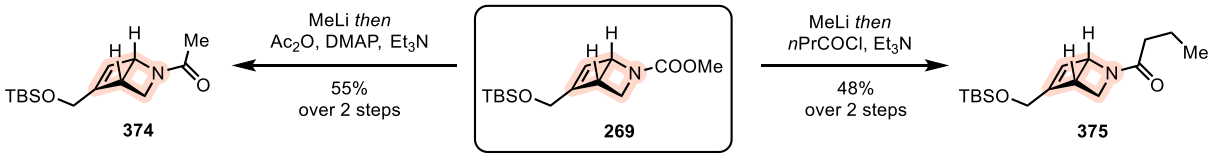
The Cbz group is a convenient nitrogen protecting group, since it can usually be removed chemoselectively with mild hydrogenolysis. However, catalytic hydrogenation conditions were not suitable for all 2-azabicyclo[2.2.0]hexane substrates (Scheme 66).



Scheme 66: Attempts at deprotecting benzyloxycarbonyl protecting group.

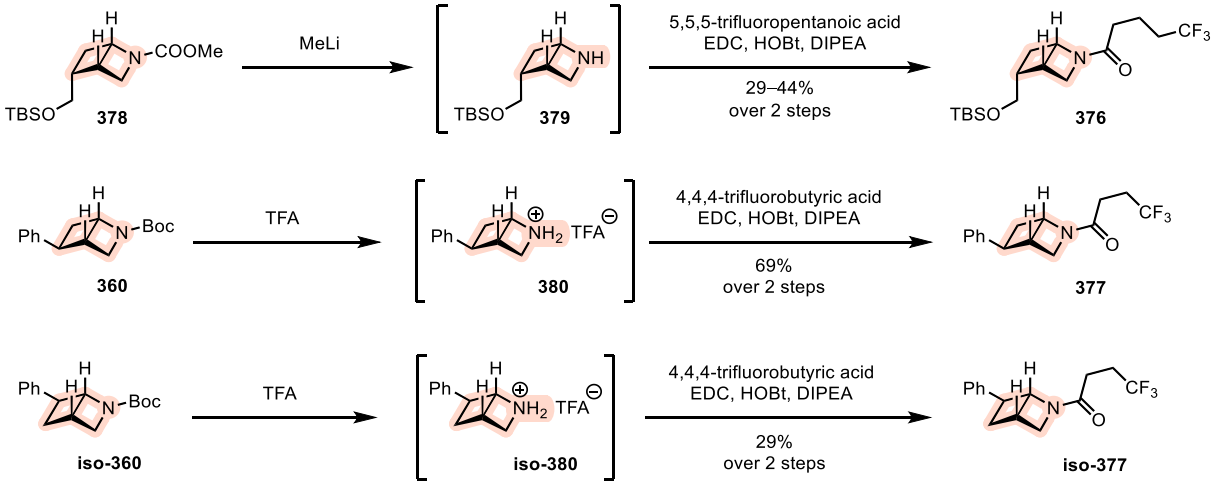
For example, if alcohol **314** was subjected to classic catalytic hydrogenation conditions with palladium on carbon in methanol, piperidine **371** was the only reaction product. This product arises from overreduction and cleavage of the central C1–C4 carbon-carbon bond. However, if alcohol **314** was protected with a bulky protecting group such as in **372**, then the same conditions furnished the desired amine **373** in almost quantitative yield (98%). Our current hypothesis is that the bulky TIPS group shields the central C1–C4 carbon-carbon bond from interacting with the active catalyst.

Due to sensitivity of carbamate-protected 2-azabicyclo[2.2.0]hex-5-enes to strong acids, compound **269** had to be deprotected with MeLi.[109] The resulting amine intermediate (not shown) was immediately treated with desired activated carboxylic acid derivatives in the presence of triethylamine and catalytic amounts of DMAP to give desired amides **374** and **375** in 55% and 48% yield, respectively (Scheme 67).



Scheme 67: Deprotection of carbamate protected 2-azabicyclo[2.2.0]hex-5-enes and amide bond formation.

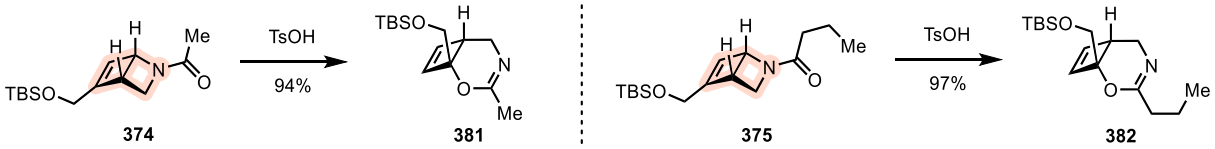
Besides aromatic carboxylic acids, aliphatic carboxylic acids like 4,4,4-trifluorobutyric and 5,5,5-trifluoropentanoic acid readily coupled with 2-azabicyclo[2.2.0]hexanes to give amides **376**, **377** and **iso-377** (Scheme 68).



Scheme 68: Carbamate removal and coupling with aliphatic carboxylic acids.

By employing MeLi, methyloxycarbonyl protecting group in **378** could be removed in one step prior to amide bond formation to yield free amine **379**, albeit resulting in a lower yield over 2 steps. TFA deprotections of *tert*-butyl carbamates **360** and **iso-360** yielded ammonium salts **380** and **iso-380**, which were without purification, coupled with 4,4,4-trifluorobutyric acid to yield fluorinated amides **377** and **iso-377** in 69% and 29% yields, respectively.

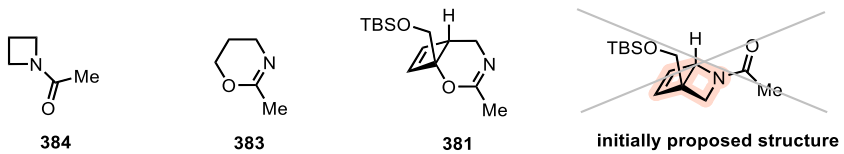
During the course of our study on amidations, an interesting rearrangement was observed. Deprotection of TBS protected allylic alcohols **374** and **375** under acidic conditions was desired. However, upon treatment of amides **374** and **375** with *p*-toluenesulfonic acid in methanol, rearranged products **381** and **382** were obtained in almost quantitative yields (94% and 97%, respectively) (Scheme 69).



Scheme 69: Unexpected rearrangement under tert-butyldimethylsilyl group deprotection conditions.

Initially mistaken for amides with a quaternary carbon atom, a closer look at NMR spectral data of these products revealed that their carbonyl ^{13}C NMR resonance shifts were inconsistent with structurally relevant compounds. The work of Nicolau et al. was instructive as he and his coworkers encountered a similar structural elucidation conundrum (Table 12).[110]

*Table 12: ^{1}H and ^{13}C NMR chemical shifts comparison between N-acylazetidine (**384**) and dihydrooxazine (**383**).*

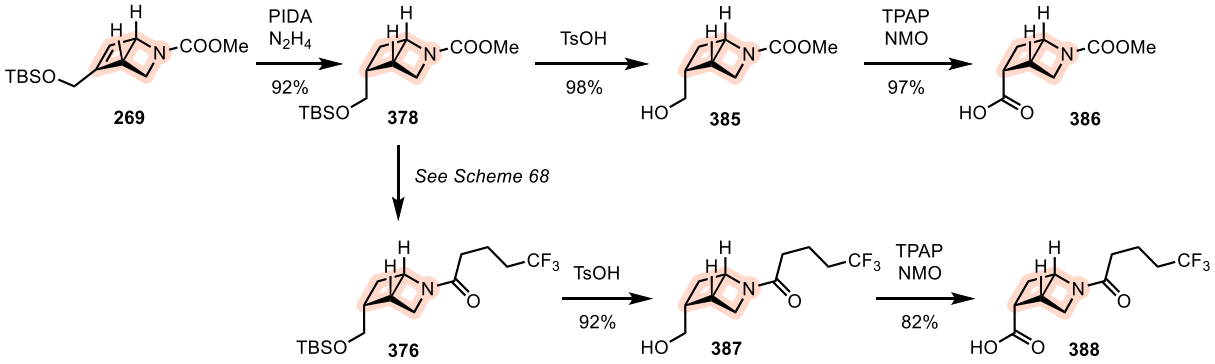


Chemical shift \ Compound	**384**	**383**	**381**
δ_{Me} in ^{1}H NMR [ppm]	1.85	1.85	1.91
$\delta_{carbonyl}$ in ^{13}C NMR [ppm]	170.4	157.4	158.2

^{13}C NMR chemical shift of the carbonyl group carbon atom in the rearranged product **381** is nearly identical to the ^{13}C NMR chemical shift corresponding carbon atom in the dihydrooxazine **383** ($\Delta\delta$ = 0.8 ppm). Carbonyl group carbon atom in *N*-acetylazetidine (**384**) resonates at 170.4 ppm ($\Delta\delta$ = 12.2 ppm).

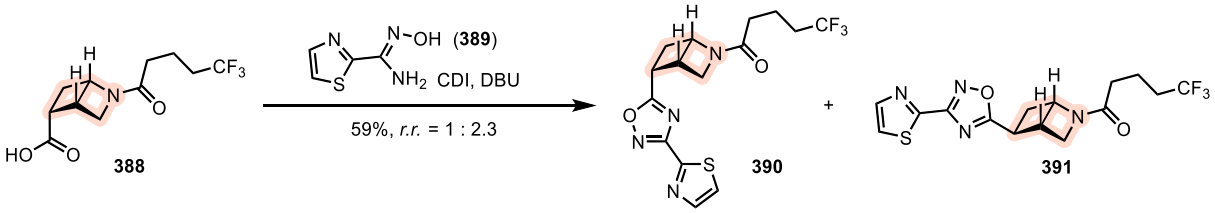
5.3. Synthesis of unnatural amino acids and diamine linkers

Unnatural amino acids are invaluable building blocks for the synthesis of complex molecules and peptidomimetic drugs. They can also be incorporated into SAR campaigns or serve as potential drugs themselves.[111] Given their utility, we wanted to synthesize amino acids with a 2-azabicyclo[2.2.0]hexane core. This was readily accomplished from 2-azabicyclo[2.2.0]hex-5-ene **269** bearing a protected hydroxymethylene side chain (Scheme 70). Diimide reduction of **269** yielded saturated derivative **378** with complete control of diastereoselectivity. Deprotection of the TBS group with *p*-tolueneulfonic acid furnished primary alcohol **385** in almost quantitative yield (98%). Oxidation of the aforementioned alcohol was most readily achieved with 10 mol% TPAP in the presence of large excess of NMO. The coveted amino acid **386** was obtained in 97% yield. The same sequence of operations could be performed on amide **376.** TBS deprotection was just as facile and alcohol **387** was oxidized to the corresponding acid **388** in 82% yield.



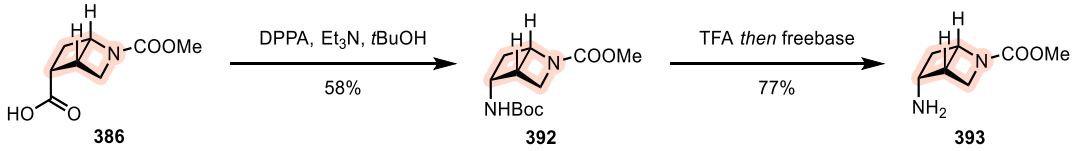
*Scheme 70: Synthesis of carboxylic acids **386** and **388**.*

In 2014, 59% of all FDA-approved small molecule drugs contained a nitrogen heterocycle.[1] Carboxylic acids can serve as convenient precursors for heterocycle synthesis. To illustrate this, carboxylic acid **388** was condensed with amidoxime **389**[112] to give a 1 : 2.3 mixture of 1,2,4-oxadiazoles **390** and **391** in 59% combined yield (Scheme 71). While epimerization at C5 was unexpected, our goal of demonstrating the utility of carboxylic acid as a functional handle for heterocycle synthesis was accomplished. While unexpected, this epimerization does facilitate rapid access to both C5 diastereomers, which could prove fruitful in SAR studies in a drug discovery setting. Additional work is required to identify reaction conditions for epimerization-free coupling and condensation.



*Scheme 71: Heterocycle formation via condensation with amidoxime **389**.*

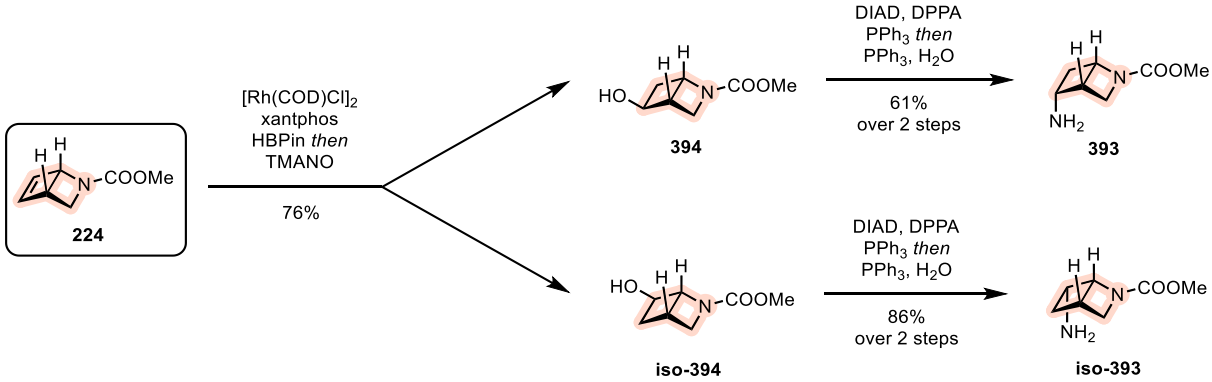
Next, we explored the venerable Curtius rearrangement on carboxylic acid **386** as we wanted to synthesize a diamine linker based on 2-azabicyclo[2.2.0]hexane scaffold (Scheme 72).



Scheme 72: Curtius rearrangement and removal of tert-butyloxycarbonyl group.

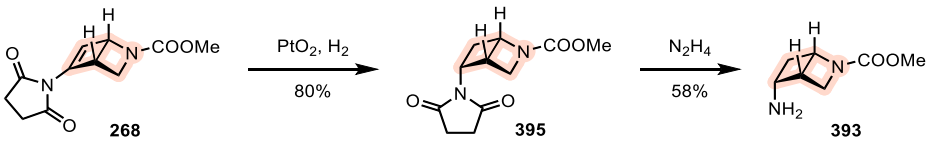
The highest yields of bis-carbamate **392** were obtained by refluxing carboxylic acid **386** with DPPA and Et_3N in a mixture of *tert*-butanol and CCl_4. The *tert*-butyloxycarbonyl group was then removed with TFA and the resulting ammonium salt (not shown) was freebased by passing the crude product through a column of silica with aqueous ammonia-containing mobile phase to yield the desired monoprotected diamine **393** in 45% yield over two steps.

Since three steps are required to synthesize carboxylic acid **386** from 2-azabicyclo[2.2.0]hex-5-ene **269**, a shorter route towards the diamine above **392** was sought (Scheme 73). We envisioned first, activation of an installed alcohol followed by substitution with a sufficient nitrogen nucleophile. One pot oxidative hydroboration of **224** yielded a mixture of alcohols **394** and **iso-394** in 90% combined yield. Alcohols **394** and **iso-394** were separated using conventional column chromatography and separately subjected to Mitsunobu inversion and Staudinger reduction conditions. C5-alcohol **394** gave us 61% yield of the desired amine **393** over 2 steps. Its constitutional isomer **iso-393**, prepared from C6-alcohol **iso-394**, was synthesized in 86% yield over 2 steps.



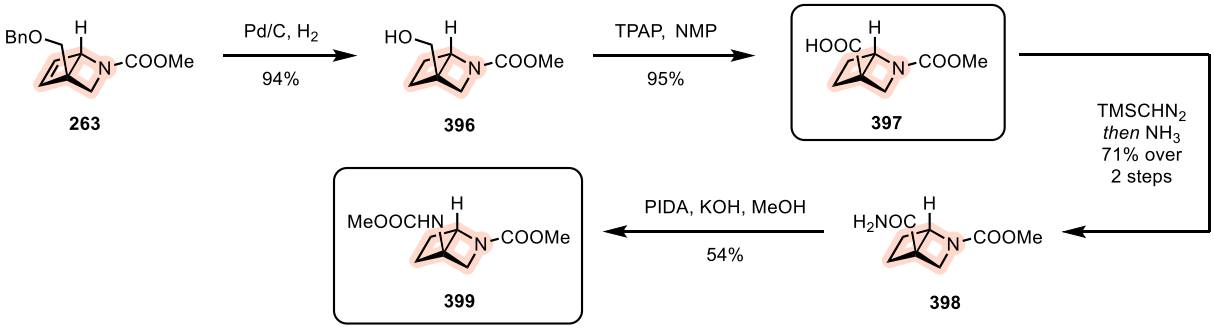
*Scheme 73: Divergent synthesis of amines **393** and iso-**393**.*

The fastest route to the C5-monoprotected diamine **393** was established from 2-azabicyclo[2.2.0]hex-5-ene **268** by screening reduction and deprotection conditions (Scheme 74Scheme 73). Reduction attempts of **268** with diimide (generated either from hydrazine or from potassium azodicarboxylate) gave complex mixtures. The same result was obtained with catalytic hydrogenation by using rhodium on carbon, rhodium on alumina, or Adams' catalyst in methanol. Gratifyingly, the use of Adams' catalyst in ethyl acetate as a solvent resulted in a clean formation of the desired succinimide **395** in 80% yield as a single constitutional isomer. Succinimide deprotection was then attempted with ethylene diamine and anhydrous hydrazine. Only by using an excess amount of anhydrous hydrazine in refluxing methanol were we able to obtain the desired monoprotected diamine **393** in 58% yield. The uniqueness of these conditions to effect the desired transformation is emphasized by the fact that heating succinimide **395** in neat ethylene diamine at 90 °C did not result in desired deprotection.



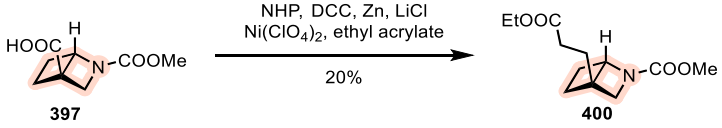
*Scheme 74: A two-step synthesis of amine **393**.*

Constitutional isomers of amino acids and diamines at C4-position were targeted next (Scheme 75). Starting from C4-substituted 2-azabicyclo[2.2.0]hex-5-ene **263** with a benzyl protected hydroxymethylene group, debenzylation under catalytic hydrogenolysis conditions yielded saturated alcohol **396** in 94% yield. The latter could be directly transformed into protected amino acid **397** in 95% yield under Ley-Griffith oxidation conditions. Since all our Curtius rearrangement attempts were unsuccessful, Hofmann rearrangement was chosen as an alternative. Towards this goal, amino acid **397** had to be transformed into the corresponding carboxamide **398**. This seemingly simple task was not straightforward and had to be performed stepwise. All our attempts to activate the amino acid **397** and couple it with ammonia as a nucleophile were low yielding. Fortunately, a two-step protocol consisting of methylation with $TMSCHN_2$ and ammonolysis with saturated methanolic ammonia yielded the desired carboxamide **398** in 71% yield. Finally, Hofmann rearrangement with PIDA and potassium hydroxide proceeded uneventfully to give doubly protected diamine **399** in 54% yield. Our protecting group strategy needs to be adjusted in the future to obtain a synthetically more valuable diamine linker with orthogonal protecting groups, allowing its users to deprotect primary and secondary amine moieties in a controlled and stepwise manner.



*Scheme 75: Synthesis of carboxylic acid **397** and Hofmann rearrangement.*

Baran's nickel catalyzed one pot Barton decarboxylation and Giese addition reaction was briefly explored with amino acid **397** (Scheme 76).[113]



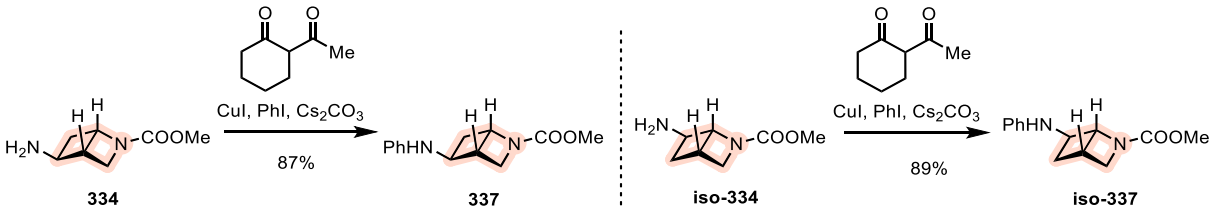
Scheme 76: Thermal nickel catalyzed Barton decarboxylation and Giese addition.

We isolated the two-carbon homologated ester **400**, albeit in only 20% yield. Since this reaction was also plagued by low reproducibility, more efforts will be put forward to address the source of these issues.

After developing routes to 5 different (protected) amino-2-azabicyclo[2.2.0]hexanes **334**, **iso-334**, **393**, **iso-393** and **399**, we then turned towards exploring suitable *N*-arylation protocols.

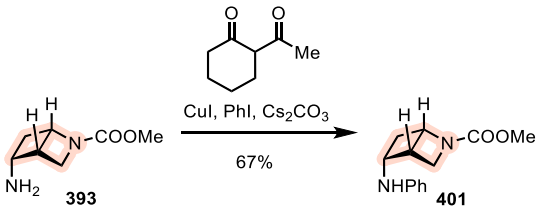
5.4. *N*-arylation

Initial attempts to arylate amines **334** and **iso-334** under Chan-Lam conditions were unsuccessful, as low mass balances were obtained and the corresponding products were contaminated with side products or excess reagents. Buchwald's *N*-arylation protocol with ethylene glycol as a ligand (at elevated temperatures) was examined next.[114] To our surprise, the main reaction pathway was ligand arylation. A closer look at the literature revealed that room temperature *N*-arylation is possible by employing copper catalysis with 1,3-diketones as ligands.[115] Gratifyingly, application of Buchwald's room temperature conditions cleanly furnished arylated amines **337** and **iso-337** in 87% and 89% yield, respectively (Scheme 77).



*Scheme 77: Room temperature N-arylation of amines **334** and **iso-334** under Buchwald's copper-catalyzed conditions.*

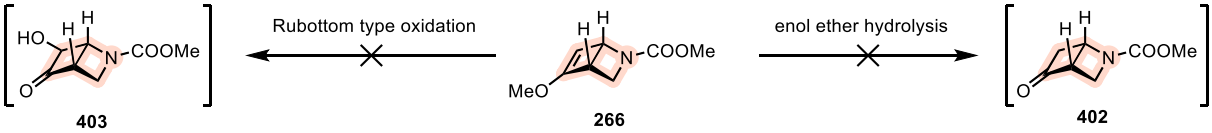
These conditions also performed well on the C5-substituted 2-azabicyclo[2.2.0]hexane with the amino group on the concave face **393**. The corresponding arylated product **401** was isolated in 67% yield (Scheme 78).



*Scheme 78: Room temperature N-arylation of amins **393** under Buchwald's copper-catalyzed conditions.*

5.5. Carbonyl chemistry

We were next interested in exploring the synthetic utility of methyl vinyl ether **266**. Hydrolysis of this product could lead to the more synthetically useful ketone **402** (Scheme 79). Unfortunately, our hydrolysis attempts were unsuccessful as they led to decomposition, attributed to the instability of the desired ketone **402** *(vide infra)*. Similarly, Rubottom-type oxidation attempts to access a higher oxidation state derivative **403** were also met with failure. Further studies on hydrolysis and oxidation of methyl ether **266** are warranted.

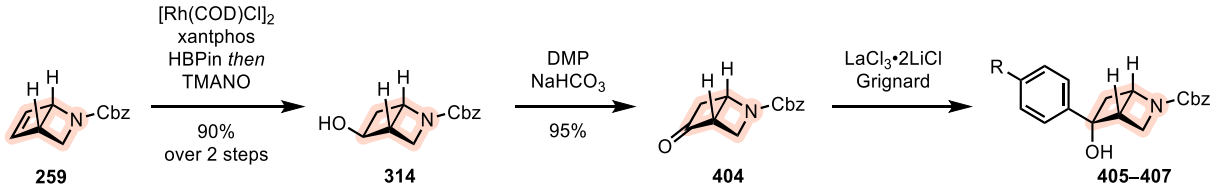


*Scheme 79: Attempted oxidation and hydrolysis of methyl vinyl ether **266**.*

Inspiration for another route to the desired ketone **402** came from Herzon's group.[116] When HAT hydration of vinyl bromide (**265**) was attempted, complete consumption of starting material was observed. The desired ketone **402** could be detected with TLC and ^{1}H NMR analysis; however, its

instability towards column chromatography prevented us from isolating it in synthetically useful yields.

As a workaround to these challenges, a new route to the benzyloxycarbonyl protected ketone **404**, relying on oxidation of the C5-alcohol **314**, was envisioned (Scheme 80). While Parikh-Doering oxidation led to decomposition, Dess-Martin oxidation of alcohol **314** with DMP gave the desired ketone **404** in 95% yield (Scheme 80). A slight modification of the extraction- and column chromatography-free workup procedure from Yao et al. was crucial for obtaining ketone **404** in high yield.[117] The limited stability of the ketone **404** manifested itself in the following modest yielding Grignard addition step as well.



*Scheme 80: Synthetic workflow for accessing tertiary alcohols **405**–**407**.*

4-chlorophenylmagensium bromide was selected as our Grignard reagent of choice for 1,2-addition optimization. Careful temperature control was required as letting the reaction mixture warm up above cryogenic temperatures led to decomposition. By quenching the reaction mixture at -78 °C, 35% NMR yield of the desired product (**405**, R=Cl) was obtained (Table 13, entry 1). According to Inamoto et al.'s original report, adding anhydrous $CeCl_3$ slightly improved the reaction yield (Table 13, entry 2).[118] To improve reaction homogeneity, Knochel's system with added LiCl was evaluated.[119] Lewis acid equivalents (1 or 2.5) and the order of reagent addition were examined next (Table 13, entries 3–6). As excess of $LaCl_3$·2LiCl was detrimental to the reaction yield, we settled upon adding 1 equivalent of the Lewis acid to the ketone **404** (normal order of addition).

Table 13: Optimization of 1,2-Grignard addition.

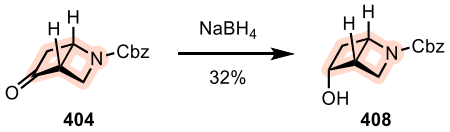
Entry	Additive	Additive eq.	Order of addition	**405** NMR yield [%]
1	/	/	/	35
2	$CeCl_3$	1	Inverse	44
3	$LaCl_3$·2LiCl	1	Normal	47
4	$LaCl_3$·2LiCl	1	Inverse	35
5	$LaCl_3$·2LiCl	2.5	Normal	34
6	$LaCl_3$·2LiCl	2.5	Inverse	39

With optimized reaction conditions in hand, two additional aryl Grignard reagents were evaluated (Table 14, entries 1–3). As ketone **404** purification was generally avoided, yields are reported over two steps from alcohol **314**.

Table 14: Overall yields for alcohol oxidation and 1,2-Grignard addition.

Entry	R	Product	Yield over 2 steps [%]	Yield average [%]
1	Cl	**405**	30–61	40
2	Me	**406**	24–43	33
3	H	**407**	53	53

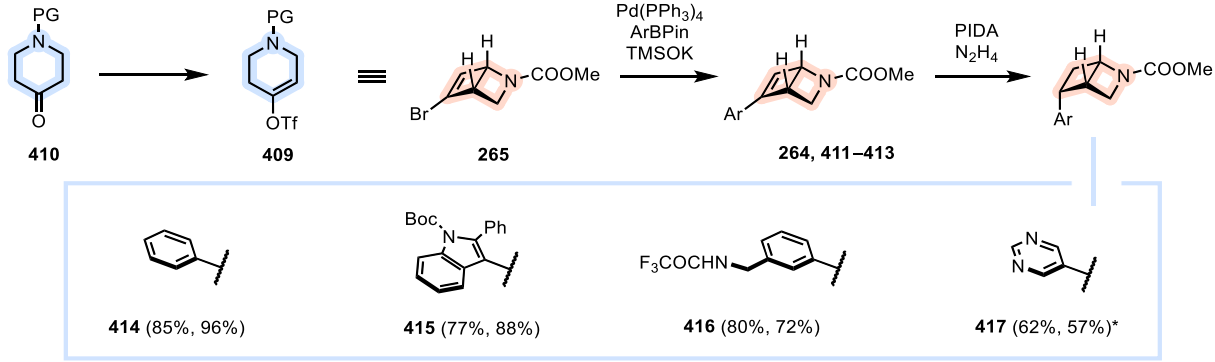
Ketone **404** could also be reduced with sodium borohydride to access the "pseudoaxial" C5-alcohol **408**, albeit in only 32% yield (unoptimized) (Scheme 81).



*Scheme 81: Reduction of ketone **404**.*

5.6. Suzuki coupling

On the other hand, vinyl bromide (**265**) could be successfully employed in Suzuki-Miyaura coupling reactions (Scheme 82). This building block, conveniently prepared in two steps from commercially available starting materials, serves as a synthetic equivalent to vinyl triflate **409**. This triflate, derived from 4-piperidone **410**, has historically presented a gateway to the privileged class of 4-(hetero)aryl substituted piperidine drugs.

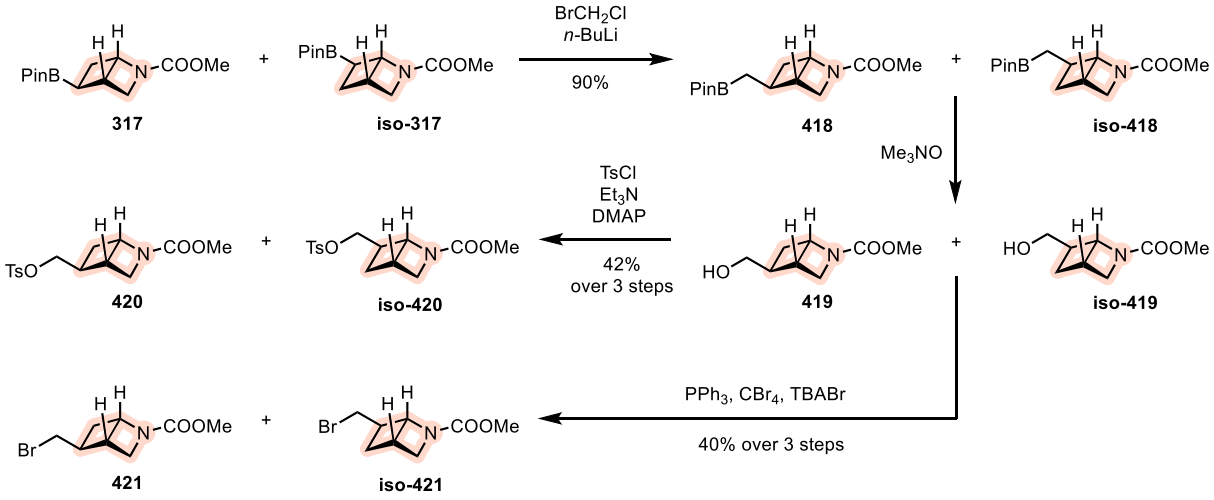


*Scheme 82: Synthetic workflow for preparation of arylated 2-azabicyclo[2.2.0]hexanes with aryl substituents in the "pseudoaxial" position.*3 mol% Pd-CataCXium A-G3, 1.1 eq. ArBNeo, 1.5 eq. TMSOK, 3 eq. $B(OMe)_3$*

Following reports from the Denmark lab, we were drawn towards potassium trimethylsilanoate as a convenient and homogenous base for Suzuki-Miyaura cross-couplings.[120] In combination with $Pd(PPh_3)_4$, various aryboronic acid pinacol esters could be coupled with vinyl bromide **265** to yield styrenes **411**–**413** (not shown) in 77–85% yields. After diimide reduction, 2-azabicyclo[2.2.0]hexanes bearing phenyl (**414**), 3-indolyl (**415**) or 3-((2,2,2-trifluoroacetamido)methyl)phenyl (**416**) substituents at C5-positions were obtained with perfect diastereoselectivity in 72–96% yields (Scheme 82). This sequence of transformations ensures that aryl substituents end up on the concave face of the bicycle and is therefore complimentary to reductive Heck and dual photo/nickel catalyzed cross-couplings, which install aryl groups on the convex face. Due to challenges associated with several heteroaryl boronic acid derivatives in palladium-catalyzed reactions, the combination of pyrimidine-5-boronic acid neopentylgycol ester, trimethylborate and Pd-CataCXium A-G3 had to be employed to access pyrimidine **417**.[121]

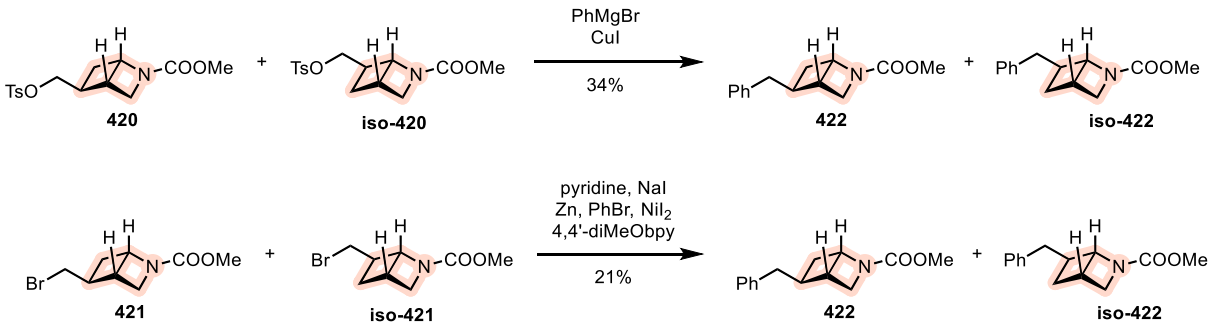
5.7. Synthesis of electrophiles

Besides being competent coupling partners for dual photo/nickel catalyzed cross-coupling, boronic acid pinacol esters **317** and **iso-317** could be homologated under Matteson's conditions. Treating a solution of the esters **317**, **iso-317**, and bromochloromethane with 1.6 M *n*-BuLi solution and warming it up from -78 °C to room temperature led to, after silica plug filtration, a mixture of homologated boronic acid pinacol esters **418** and **iso-418** in 94% yield (Scheme 83). Their separation was not attempted. They could be oxidized to the corresponding alcohols **419** and **iso-419**. Since the isolation of the aforementioned alcohols was complicated by the presence of pinacol, we isolated the corresponding tosylates **420** and **iso-420** or bromides **421** and **iso-421** instead.



Scheme 83: Matteson homologation, oxidation with Me_3NO and synthesis of electrophiles.

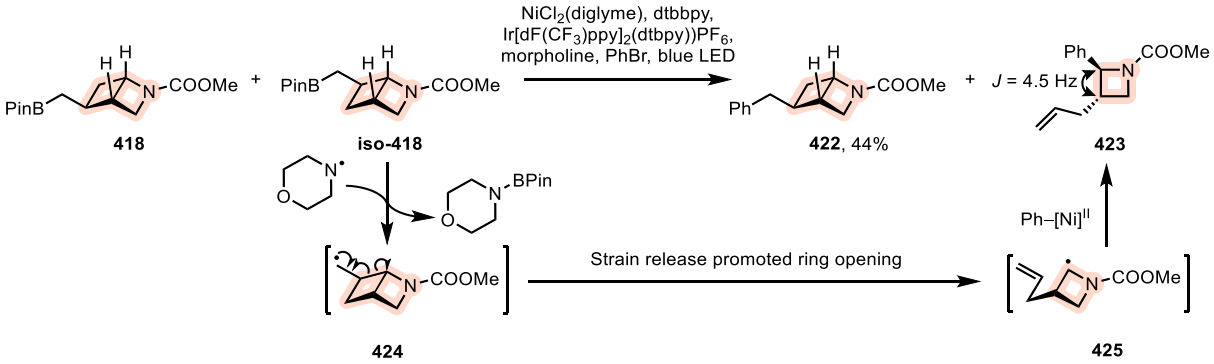
With the mixtures of tosylates (**420** and **iso-420)** and bromides (**421** and **iso-421**) in hand, we wanted to synthesize 2-azabicyclo[2.2.0]hexanes **422** and **iso-422** with phenylmethylene substituents. Two strategies were evaluated, depicted in Scheme 84. The mixture of tosylates **420** and **iso-420** was exposed to phenylmagnesium bromide in the presence of copper(I) iodide. The desired products were obtained in 34% combined yield. Hayashi's protocol with 5 mol% $Fe(acac)_3$ in refluxing Et_2O gave inferior results.[122] The mixture of bromides **421** and **iso-421**, on the other hand, was engaged in Weix's cross-electrophile coupling with bromobenzene in the presence of pyridine, sodium iodide, zinc, nickel(II) iodide and 4,4'-dimethoxyl-2,2'-dipyridyl.[123] The desired products **422** and **iso-422** were obtained in 21% combined yield.



*Scheme 84: Nucleophilic displacement and cross electrophile coupling attempts for accessing **422** and **iso-422**.*

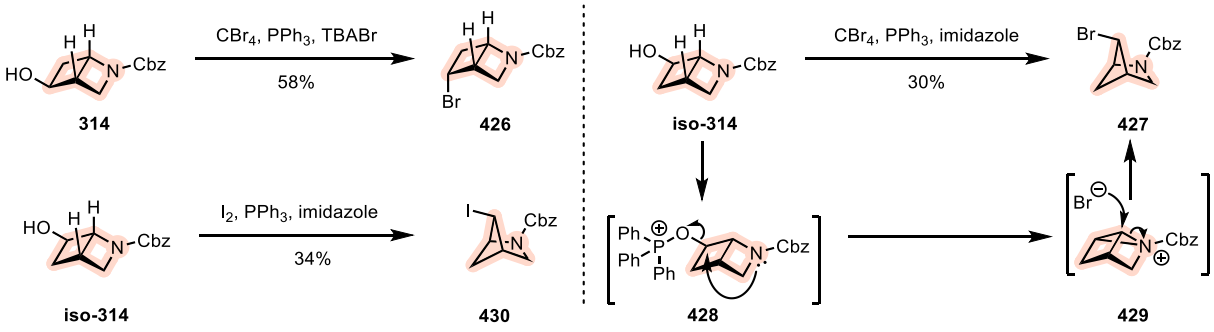
Given the low yields of cuprate nucleophilic substitution and cross-electrophile coupling, the dual photo/nickel catalyzed cross-coupling between homologated boronic acid esters **418** and **iso-418** and bromobenzene (Scheme 85) was explored next. We decided to use excess of bromobenzene because

the homologated esters were more precious to us. Despite this deviation from reported conditions, the reaction still performed adequately. Surprisingly, the desired 2-azabicyclo[2.2.0]hexane **422** was isolated alongside azetidine **423**. The proposed mechanism for its formation starts by an *N*-centered radical cleaving the C–B bond and generating primary radical **424** and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)morpholine byproduct. The former undergoes strain-release-promoted ring opening to afford stabilized secondary α-amino radical **425**. This radical is then intercepted by the nickel species and gives, after reductive elimination, the unexpected product (**423**). The *trans*-relationship between phenyl and ally substituents was determined based on the small value of the coupling constant between adjacent protons (J = 4.5 Hz).



Scheme 85: Dual photo/nickel catalyzed cross-coupling between homologated boronic acid pinacol esters and bromo benzene.

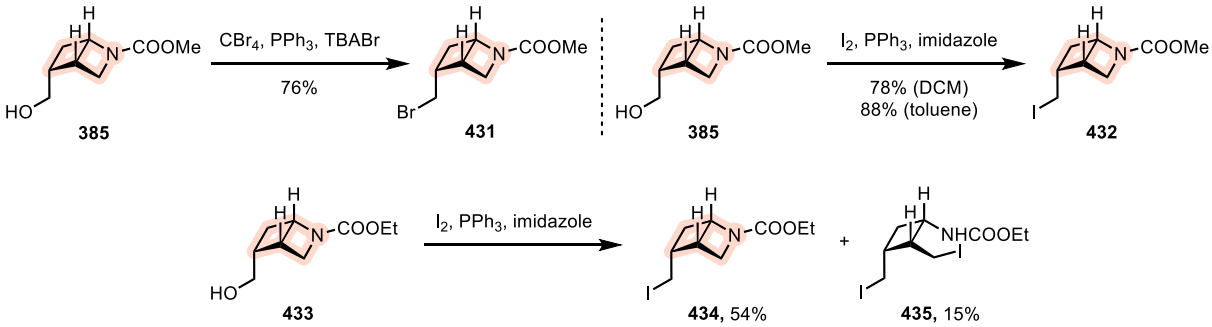
Having established concise routes to various 2-azabicyclo[2.2.0]hexanes bearing hydroxyl groups, we wanted to exploit those groups for the preparation of 2-azabicyclo[2.2.0]hexanes with halogen substituents, as these could be useful electrophiles for amine alkylation and other nucleophilic substitution reactions. Under Appel conditions with catalytic tetrabutylammonium bromide, C5-alcohol **314** was transformed into bromide **426** in 58% yield (Scheme 86). The same conditions could not be directly applied to C6-alcohol **iso-314**, instead requiring elevated temperatures to react. However, the bromide **427** that formed in 30% yield was not the expected product. A rearrangement of the 2-azabicyclo[2.2.0]hexane scaffold occurred. Presumably, the neighboring carbamate displaces the activated alcohol in intermediate **428**. The bromide anion then attacks the resulting cationic species **429** to give the 2-azabicyclo[2.1.1]hexane scaffold **427**. When carbon tetrabromide was replaced with iodine, the corresponding iodide **430** was formed in 34% yield. These observations are consistent with Krow's work, and our spectral data matches closely with reported values for related products.[124]



*Scheme 86: Reactivity of alcohols **314** and **iso-314** under Appel conditions.*

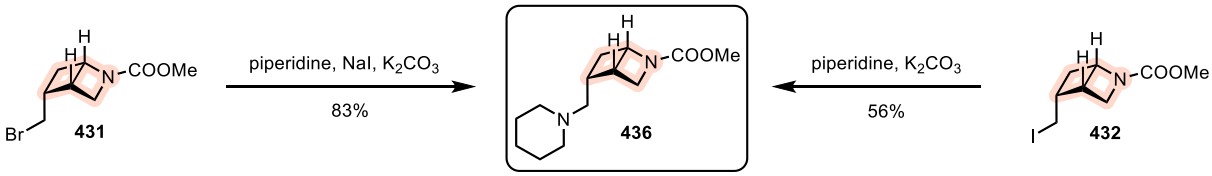
Alcohol **385**, depicted in Scheme 87, was converted into the corresponding bromide **431** and iodide **432** in 76% and 88% yields, respectively. For the installation of iodide **432**, toluene afforded a cleaner

reaction profile and higher yield, compared to DCM. When the same transformation was attempted on ethyloxycarbonyl protected alcohol **433**, only 54% yield of the desired iodide **434** was obtained. Some of the remaining mass balance could be accounted for by isolation of diiodide **435** side product, which formed in 15% yield. Whether this side reactivity is a consequence of a different nitrogen protecting group or imperfect replication of initial reaction conditions cannot be ascertained as more data points are required.



Scheme 87: Synthesis of bromides and iodides.

N-alkylation of piperidine was chosen to showcase the utility of bromide **431** and iodide **432** as competent alkylating reagents (Scheme 88).

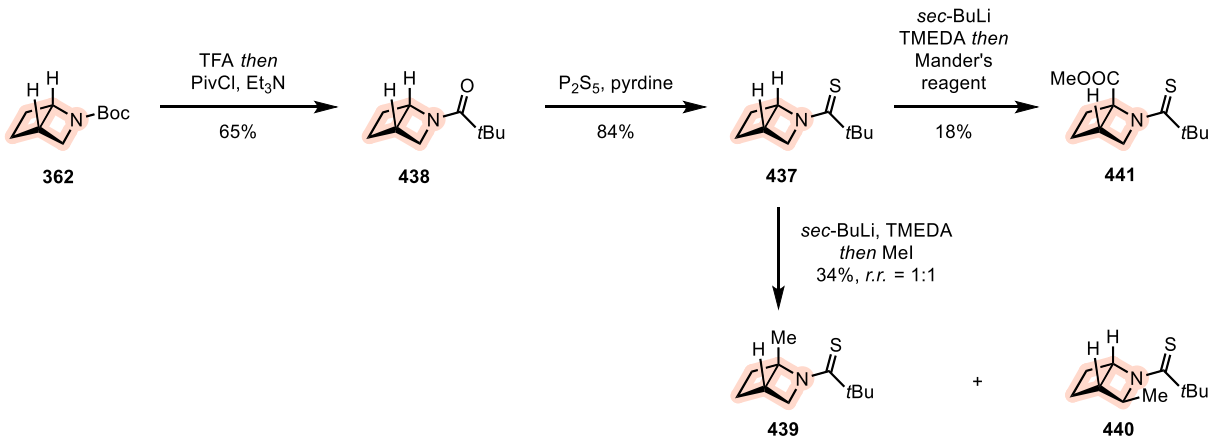


*Scheme 88: Piperidine alkylation with bromide **431** and iodide **432**.*

Stirring iodide **432** with excess of piperidine and potassium carbonate at room temperature afforded 56% yield of the desired amine **436**. By adding sodium iodide and increasing the reaction temperature, bromide **431** was engaged in the alkylation as well and afforded 83% yield of tertiary amine **436**.

5.8. C1 functional groups

Given the failure of C6-substituted 1,2-dihydropyridines to undergo 4π-electrocyclization and produce C1-substituted 2-azabicyclo[2.2.0]hex-5-enes, we attempted to install C1 functionality after the 4π-electrocyclization step. We were drawn towards the work of Hodgson et al. on directed lithiation of protected azetidines.[125] Thioamide **437** was prepared from *tert*-butyloxycarbonyl protected 2-azabicyclo[2.2.0]hexane **362** in 3 steps. (Scheme 89).



*Scheme 89: Synthesis of thioamide **437** and directed lithiation / electrophile trapping attempts.*

Tert-butyloxycarbonyl group was removed with TFA and the resulting trifluoroacetate salt (not shown) was acylated with pivaloyl chloride and excess triethylamine to yield amide **438** in 65% yield over 2 steps. Heating amide **438** with diphosphorus pentasulfide and pyridine gave, after aqueous workup and column chromatography, the desired thioamide **437** in 84% yield. Directed lithiation with *sec*-BuLi and TMEDA furnished, after quenching with methyl iodide, an inseparable mixture of C1 and C3-methylated 2-azabicyclo[2.2.0]hexanes **439** and **440** in 1 : 1 ratio and in 34% combined yield. Since methyl groups are of little synthetic utility, trapping of the putative lithiated species (not shown) with Mander's reagent was attempted. Despite several attempts to optimize the yield of this transformation, no more than 18% isolated yield of the desired amino acid derivative **441** could be obtained (Table 15). These attempts included shortening lithiation time to 5 min (Table 15, entry 1), performing a gradual warmup of the reaction mixture (Table 15, entry 2), extending lithiation time to 1 h (Table 15, entry 3), using a large excess of *sec*-Buli, TMEDA and Mander's reagent (entry 4), allowing the lithiation step to warm up to -30 °C before adding the electrophile at – 78 °C (Table 15, entry 5), performing lithiation at -100 °C (Table 15, entry 6) and using methyl chloroformate instead of Mander's reagent (Table 15, entry 7).

Table 15: Optimization of directed lithiation / electrophile trapping sequence.

Entry	**Deviation from standard conditions**	**441 NMR Yield [%]**
1	Lithiation for 5 min	14
2	Slow warmup with electrophile	16
3	Lithiation for 60 min	21
4	Excess *sec*-BuLi, TMEDA, Mander's reagent	27
5	Lithiation warm-up to -30°C	26
6	Lithiation at -100°C	18
7	MeOCOCl instead of Mander's reagent	17*

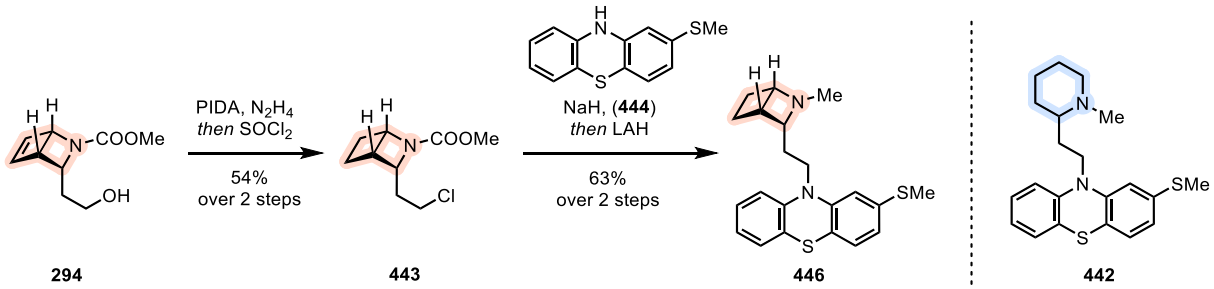
* Isolated yield

6. ISOSTERE SYNTHESIS

By extensively studying the reactivity of 2-azabicyclo[2.2.0]hex-5-enes and their saturated counterparts, we became confident that we could apply our knowledge of their behavior to the synthesis of piperidine containing drugs and drug candidate isosteres.

6.1. Thioridazine isostere

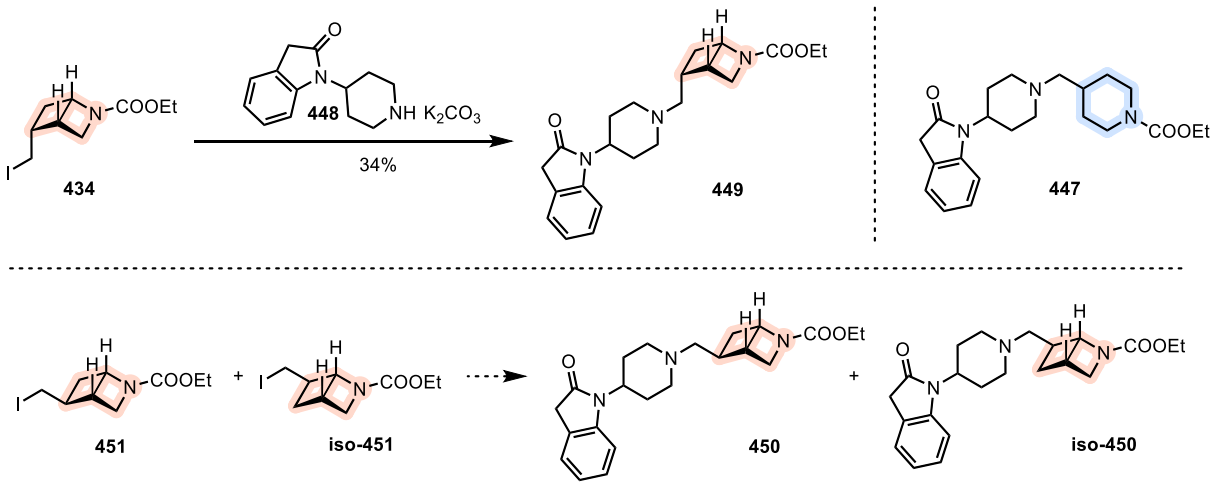
Thioridazine **442** is an antipsychotic drug for the treatment of generalized anxiety disorder and schizophrenia. Its 2-azabicyclo[2.2.0]hexane isostere was prepared from alcohol **294** in 4 steps (Scheme 90). Diimide reduction followed by chlorination with thionyl chloride furnished primary chloride **443** in 54% yield over 2 steps. 2-methylthiophenothiazine **444** was deprotonated with sodium amide in refluxing toluene and then used to substitute the primary chloride **443**. Final LAH reduction of carbamate **445** (not shown) furnished thioridazine isostere **446** in 63% yield over 2 steps.



*Scheme 90: Synthesis of thioridazine isostere **446**.*

6.2. Selective muscarinic acetylcholine receptor agonist isosteres

Compound **447**, an *N*-alkylated oxindole, was an initial lead compound in search of new antipsychotics to treat schizophrenia with a new mode of action and fewer side effects.[126] It acts as a selective muscarinic acetylcholine receptor agonist for M_1 and M_4 receptors. Its uniqueness stems from the ethyl carbamate moiety, which serves as a pharmacophore. Its isostere was prepared from primary iodide **434** in one step (Scheme 91). Alkylation of piperidine **448** in the presence of potassium carbonate yielded the desired tertiary amine **449** in 34% yield.

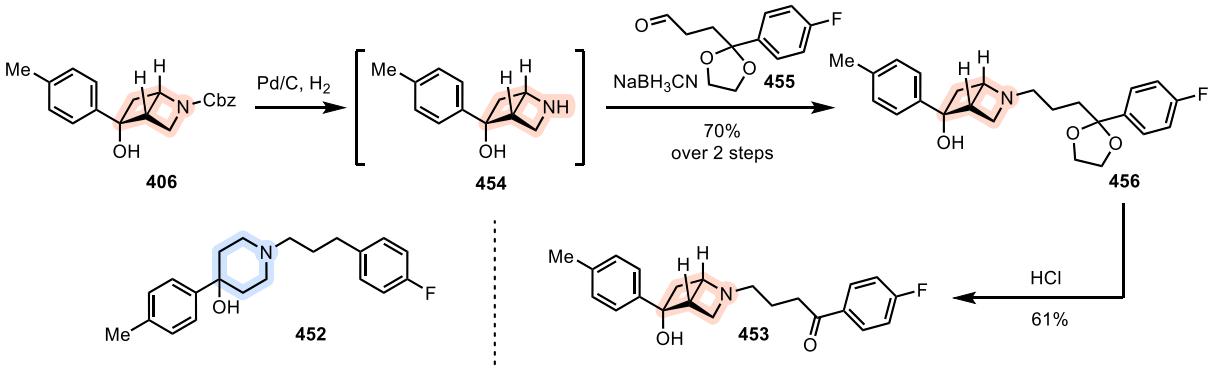


Scheme 91: Synthesis of "pseudoaxial" muscarinic acetylcholine receptor agonist isostere. Proposed synthesis of "pseudoequatorial" muscarinic acetylcholine receptor agonist isosteres.

Isostere **449** has *N*-(4-piperidinyl)oxindole moiety on the concave face of the 2-azabicyclo[2.2.0]hexane scaffold. Its "pseudoequatorial" isosteres **450** and **iso-450** with the aforementioned moiety on the convex face of the bicycle could be theoretically prepared from the mixture of primary iodides **451** and **iso-451**.

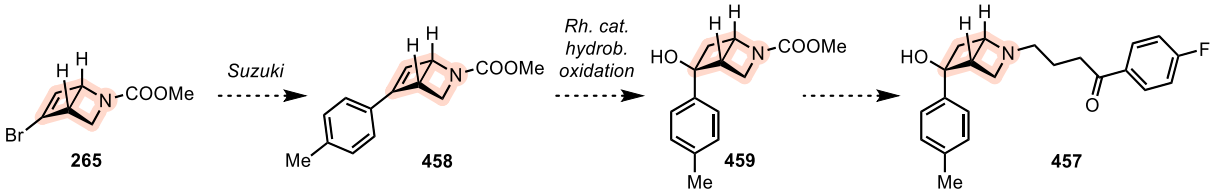
6.3. Moperone isostere

Moperone (**452**) is a neuroleptic drug from the family of butyrophenones (Scheme 92).[127] Securing access to Grignard addition product **406** was instrumental for preparing Moperone isostere **453**. Benzyloxycarbonyl deprotection with palladium on carbon and hydrogen gave, after filtration, crude amino alcohol **454**. This material was immediately subjected to reductive amination conditions without further purification. In the presence of aldehyde **455**[128] and sodium cyanoborohydride, tertiary amine **456** was obtained in 70% yield over 2 steps. Final ketal deprotection with aqueous HCl in THF afforded the desired isostere **453** in 61% yield.



*Scheme 92: Synthesis of Moperone isostere **453**.*

A synthetic plan for accessing Moperone isostere with a hydroxyl group on the concave face of the bicycle (**457**) was also envisioned (Scheme 93).



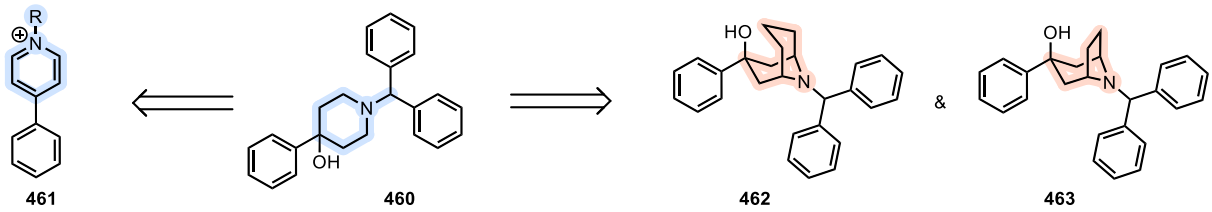
*Scheme 93: Envisioned synthetic plan for synthesizing Moperone isostere **457** with 4-methylphenyl substituent on the concave face.*

Starting from vinyl bromide **265**, Suzuki coupling with 4-methylphenylboronic acid pinacol ester would give styrene **458**. Next, rhodium-catalyzed hydroboration and one pot oxidation would then give tertiary alcohol **459**. Finally, methyloxycarbonyl group deprotection, reductive amination with aldehyde **455**, and ketal hydrolysis would give the desired compound **457**.

6.4. Nociceptin receptor ligand isosteres

The nociceptin opioid receptor was identified to be implicated in a variety of biological functions including: coughing, anxiety, pain, stress, feeding, learning, substance abuse, and has even been linked to Parkinson's disease.[129] *N*-benzhydryl substituted 4-hydroxy-4-phenylpiperidine **460** was explored as a nociceptin receptor ligand; however, the tendency of 4-aryl-4-hydroxypiperidines to be metabolized to potentially neurotoxic 4-arylpyridinium species **461** had to be addressed (Scheme 94,

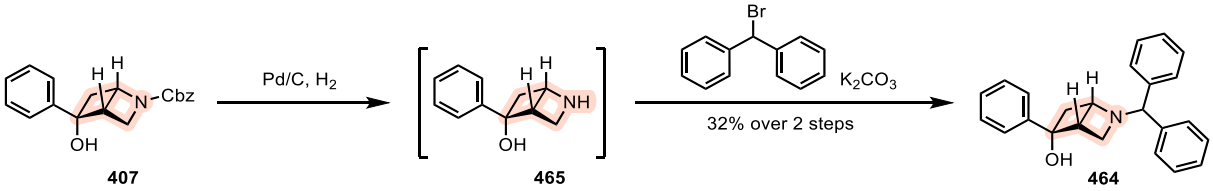
left). To this end, SAR studies led to compounds **462** and **463**, with improved affinity for nociceptin receptor (Scheme 94, right).



*Scheme 94: Metabolic fate of nociceptin receptor ligand **460** and structures of its improved bioisosteres **462** and **463**.*

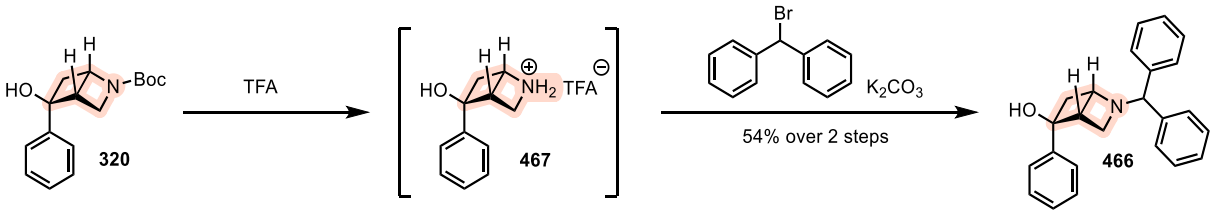
Both compounds **462** and **463** have more carbon atoms than their progenitor **460**. We envisioned that we could potentially tackle the metabolic stability issues while retaining the number of carbon atoms by isosteric replacement of the piperidine core with a 2-azabicyclo[2.2.0]hexane core.

Isostere **464** with the hydroxyl group on the concave side of the bicycle was prepared from Grignard addition product **407** in 2 steps (Scheme 95). The benzyloxycarbonyl protecting group was removed under catalytic hydrogenolysis conditions. Crude amino alcohol **465** was subjected to *N*-alkylation conditions without further purification. The combination of potassium carbonate and freshly recrystallized bromodiphenylmethane yielded the desired isostere **464** in 32% yield over 2 steps.



*Scheme 95: Synthesis of nociceptin receptor ligand isostere **464** with the phenyl substituent on the convex face of the bicycle.*

Conversely, isostere **466** with the hydroxyl group on the convex side of the bicycle, was prepared from the formal cationic rhodium-catalyzed oxidative hydroboration product **320** in 2 steps (Scheme 96). The *tert*-butyloxycarbonyl group was removed with TFA to yield trifluoroacetate salt **467**, which was used in the following step without purification. A large excess of potassium carbonate was used in the presence of freshly recrystallized bromodiphenylmethane to neutralize TFA and HBr byproducts and yield the desired isostere **466** in 54% yield over two steps.

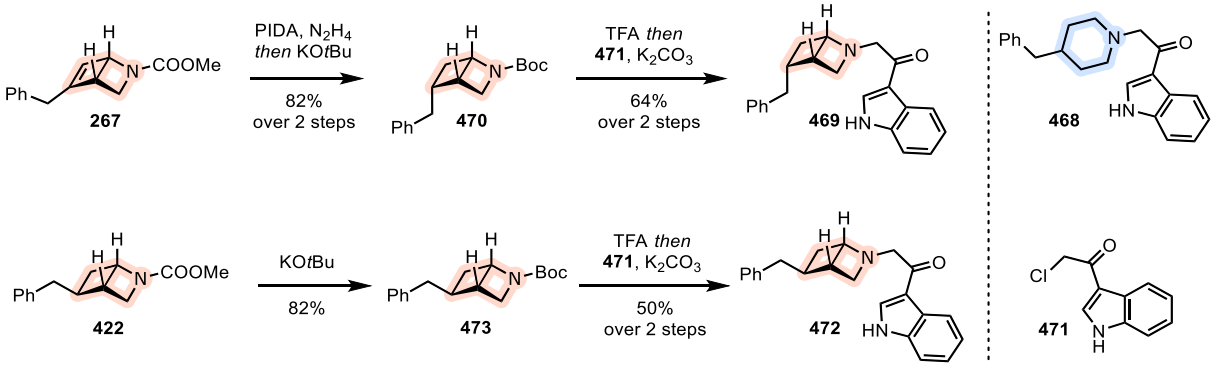


*Scheme 96: Synthesis of nociceptin receptor ligand isostere **464** with the phenyl substituent on the concave face of the bicycle.*

6.5. GluN2B/NMDAR ligand isosteres

Overstimulation of the *N*-methyl-*D*-aspartate receptors (NMDARs) leads to the activation of excitotoxic pathways and the induction of neuronal death.[130] These receptors are implicated in various neurodegenerative processes and the development of antagonists could give rise to new drugs for the treatment of brain injuries, Alzheimer's, and Parkinson's diseases. Piperidine **468** was identified as a potential agonist of the NMDAR GluN2B subunit (Scheme 97). Its 2-azabicyclo[2.2.0]hexane isosteres were synthesized from building blocks **267** and **422**.

The ”pseudoaxial” isostere **469** was prepared in a four step sequence via *tert*-butyloxycarbonyl protected **470**, which was deprotected and alkylated with α-chloroketone **471** (64% over 2 steps) (Scheme 97, top).

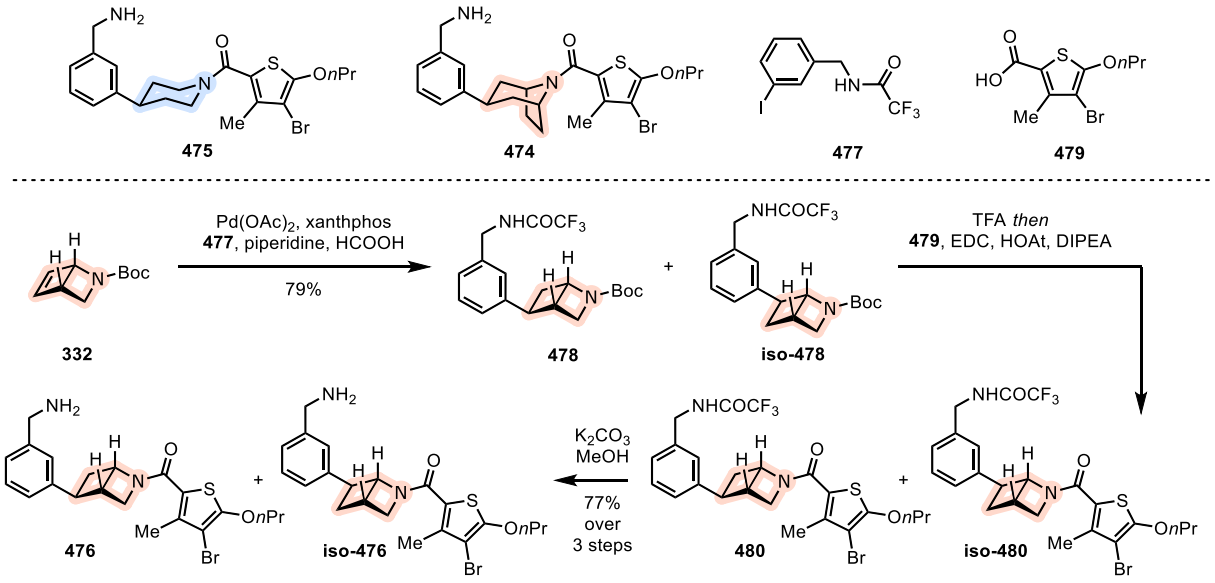


*Scheme 97: GluN2B/NMDAR ligand and its 2-azabicyclo[2.2.0]hexane-isosteres **469** and **472**.*

The “pseudoequatorial” isostere **472** was prepared analogously (Scheme 97, bottom). Protecting group exchange could be performed in 82% yield to give *tert*-butyloxycarbonyl protected derivative **473**. The subsequent deprotection and alkylation steps gave **472** in 50% overall yield.

6.6. β-tryptase inhibitor isosteres

The tropanylamide isostere **474** of β-tryptase inhibitor **475** was designed to increase the overall rigidity of the drug while limiting off-target binding to the hERG potassium channel or to cytochrome P450 enzymes.[10] We prepared three isosteres based on the 2-azabicyclo[2.2.0]hexane scaffold with the same goal in mind. Compared to tropanylamide **474**, these isosteres have two fewer carbon atoms (Scheme 98).

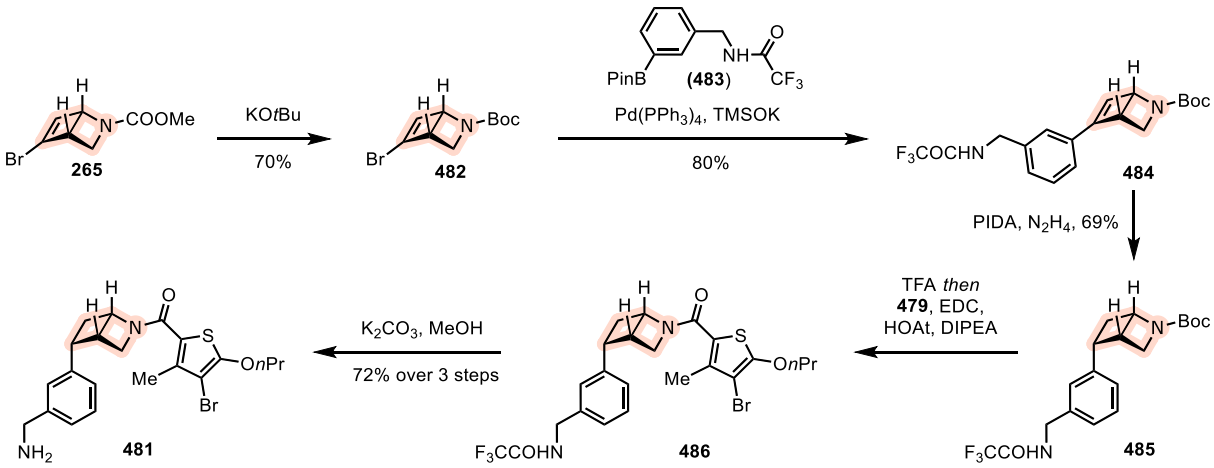


*Scheme 98: β-tryptase inhibitor and its “pseudoequatorial” isosteres **476** and **iso-476.***

The synthesis of “pseudoequatorial” isosteres **476** and **iso-476** commenced with palladium-catalyzed hydroarylation on *tert*-butyloxycarbonyl protected 2-azabicyclo[2.2.0]hex-5-ene **332**. 2,2,2-trifluoro-*N*-(3-iodobenzyl)acetamide **477** was chosen as the electrophilic coupling partner. In the presence of $Pd(OAc)_2$, xantphos, piperidine and formic acid, hydroarylated product **478** and **iso-478** were formed in a combined yield of 79%. Their ratio could not be determined from ^{1}H NMR analysis of the crude

reaction mixture due to signal overlap. These products were taken forward together because we were planning on separating the final compounds at the end. TFA deprotection of *tert*-butyloxycarbonyl protecting group and EDC-mediated coupling with thiophenecarboxylic acid **479** in the presence of HOAt and DIPEA furnished the desired mixture of amides **480** and **iso-480**. These were again taken forward as a crude mixture. The final deprotection of the trifluoroacetamide protecting group furnished the targeted amines **476** and **iso-476** in 77% yield over 3 steps.

Suzuki-Miyaura cross-coupling was chosen for the preparation of "pseudoaxial" isostere **481**. Toward this goal we required access to *tert*-butyloxycarbonyl protected vinyl bromide **482** and boronic acid pinacol ester **483**, derived from the corresponding iodide **477** (Scheme 99). To our delight, the treatment of methyloxycarbonyl protected vinyl bromide (**265**) with excess of potassium *tert*-butoxide in THF furnished the desired product **482** in 70% yield. Miyaura borylation was employed to prepare boronic acid pinacol ester **483** from iodide **477** in a single step (89% yield). The fragments were then coupled together with $Pd(PPh_3)_4$ and potassium timethylsilanoate as a homogenous base. The Suzuki coupling proceeded in 80% yield to give styrene **484**. Diimide reduction was uneventful and furnished 2-azabicyclo[2.2.0]hexane **485** in 69% yield. Like in the "pseudoequatorially" substituted compounds **478** and **iso-478**, the final three steps were performed with only one chromatographic purification. The t*ert*-butyloxycarbonyl group was removed with TFA and acid **479** was coupled onto the resulting trifluoroacetate salt (not shown). Trifluoroacetamide deprotection of **486** with potassium carbonate in methanol furnished the desired "pseudoaxial" isostere **481** in 72% yield over three steps.



*Scheme 99: Synthesis of "pseudoaxial" β-tryptase inhibitor isostere **481**.*

6.7. Fentanyl fragment isosteres

Fentanyl **487** is a small molecule drug opioid analgesic that is used for anesthesia and pain management. Since we could arylate various amino substituted 2-azabicyclo[2.2.0]hexanes, we thought we could readily access several new fentanyl isosteres. However, due to fentanyl's potency, we decided not to pursue the synthesis of final compounds **488** and **489**. This could, however, be achieved theoretically by deprotecting compounds **490** and **491** and installing the phenylethylene group on the nitrogen atom (Figure 21).

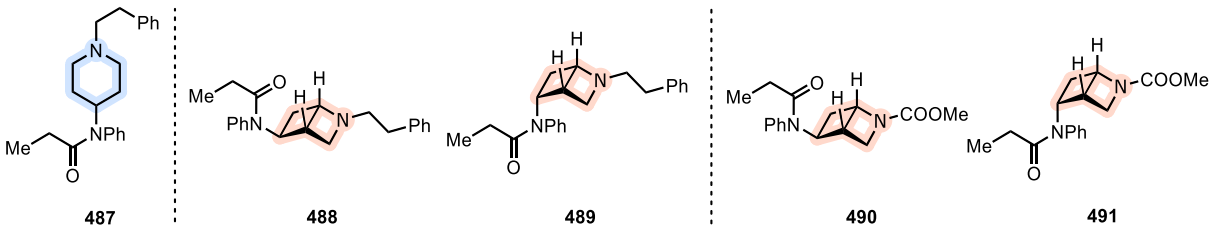
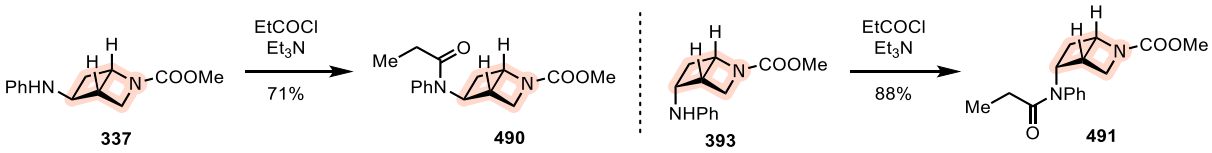


*Figure 21: Structures of fentanyl (**487**), its 2-azabicyclo[2.2.0] isosteres (**488** & **489**) and fragments **490** & **491.***

The requisite anilines **337** and **393** were acylated with propionyl chloride and triethylamine (Scheme 100). The "pseudoequatorial" aniline **337** furnished the desired amide **490** in 71% yield. The "pseudoaxial" aniline **393** gave a higher (88%) yield of the crystalline amide **491**, the structure of which was confirmed by single crystal X-ray analysis (Figure 22).



*Scheme 100: Synthesis of fentanyl isostere fragments **490** and **491**.*

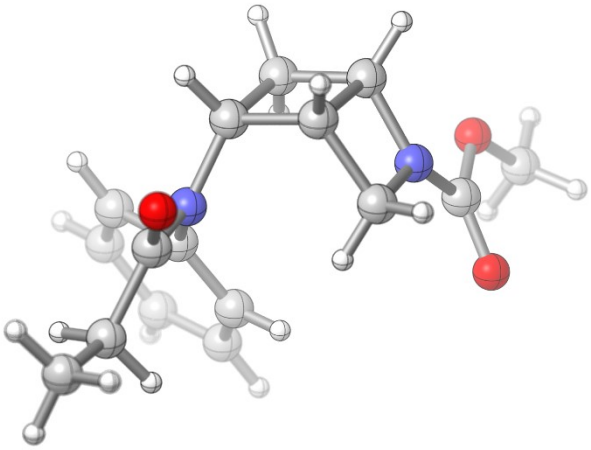
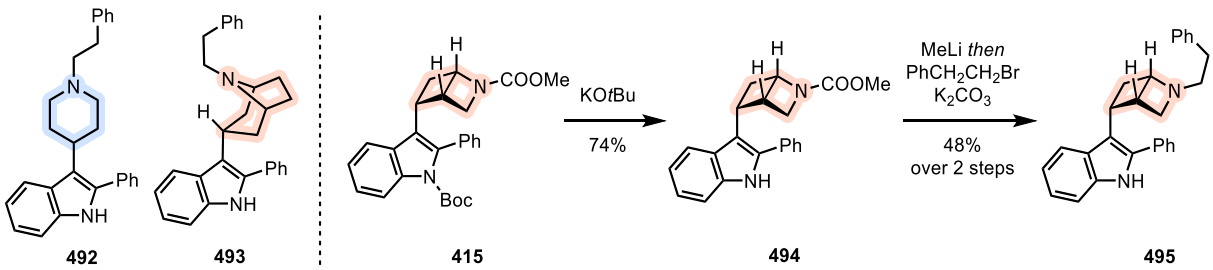


*Figure 22: Crystal structure of fentanyl isostere fragment **491**.*

6.8. h5-HT$_{2A}$ antagonist isostere

In the year 2000, selective h5-HT$_{2A}$ antagonists were sought with the aim of identifying antipsychotics for the treatment of negative symptoms of schizophrenia.[131] Towards this end, an SAR campaign elucidated two 2-phenyltryptamine derivatives with improved affinity and bioavailability based on piperidine and tropane scaffolds **492** and **493** (Scheme 101).



*Scheme 101: h5-HT$_{2A}$ antagonists **492** & **493** and their 2-azabicyclo[2.2.0]hexane isostere **495**.*

Our studies towards 2-azabicyclo[2.2.0]hexane isosteres of the aforementioned 2-phenyltryptamine derivatives began with *tert*-butyloxycarbonyl protected indole **415**. Attempted protecting group exchange on methyl carbamate led unexpectedly to free indole **494** in 74% yield. We then resorted to MeLi, which was able to remove methoxycarbonyl protecting group. The crude amine (not shown) was immediately alkylated with (2-bromoethyl)benzene to yield the ”pseudoaxial” isostere **495** in 48% yield over two steps. Due to our inability to engage 3-haloindoles in palladium-catalyzed hydroarylation or dual photo/nickel catalyzed coupling reactions (*vide supra*), an alternative set of conditions or an alternative route will have to be identified to access the corresponding “pseudoequatorial” isostere (not shown).

7. OVERVIEW OF EXPLORED 2-AZABICYCLO[2.2.0]HEXANE CHEMICAL SPACE

An overview of substituents and functional groups that we could install individually or in combination with others on the 2-azabicyclo[2.2.0]hexane scaffold is shown in the following figure (Figure 23). Synthetically tractable amine, carboxylic acid, halogen, boronic acid pinacol ester and azide functional groups could be used to adorn the 2-azabicyclo[2.2.0]hexane scaffold. These groups were amenable to subsequent transformations like oxidations, condensations, C–C couplings, C–X couplings, and nucleophilic substitutions. Several arylated 2-azabicyclo[2.2.0]hexanes, regardless of the electronic nature or substitution pattern of their aryl groups, could be accessed. All these reactions could be performed with different groups on the nitrogen atom, making it a part of carbamate, amide and tertiary amine moieties.

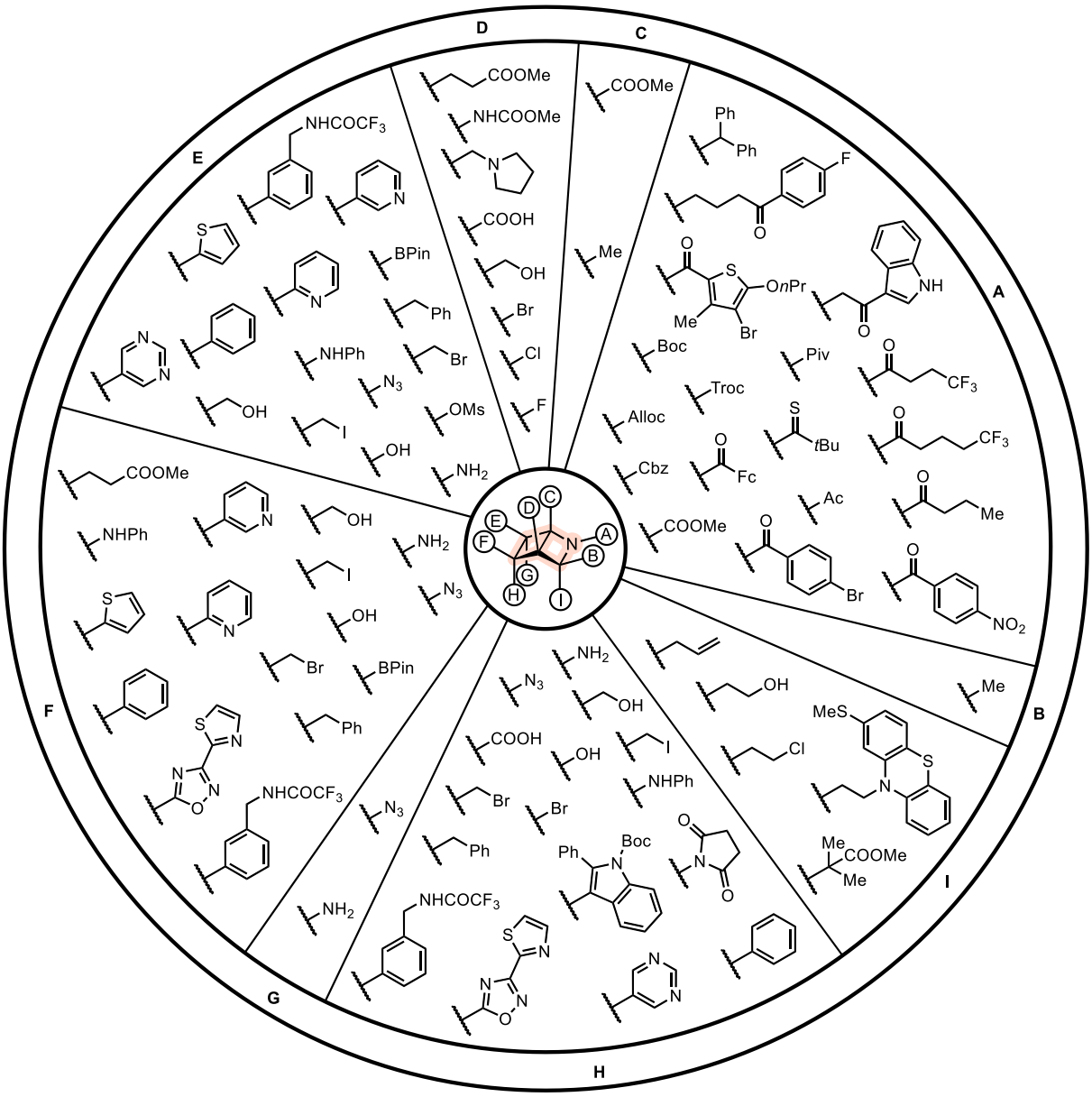


Figure 23: The explored chemical space of substituted 2-azabicyclo[2.2.0]hexanes.

Most notable are functional groups in the H section of Figure 23. These are located on the concave face of the [2.2.0] bicycle and map onto the R_2 groups of the privileged 1,4-disubstituted piperidines

in the thermodynamically less favorable axial conformation (Figure 24). As alluded to in the Introduction, these can be, in some instances, crucial for binding to the targeted receptor. However, due to facile ring flip and entropic penalty associated with it, the bioactive conformation's effective concentration is low, resulting in lower binding affinity and diminished efficacy.

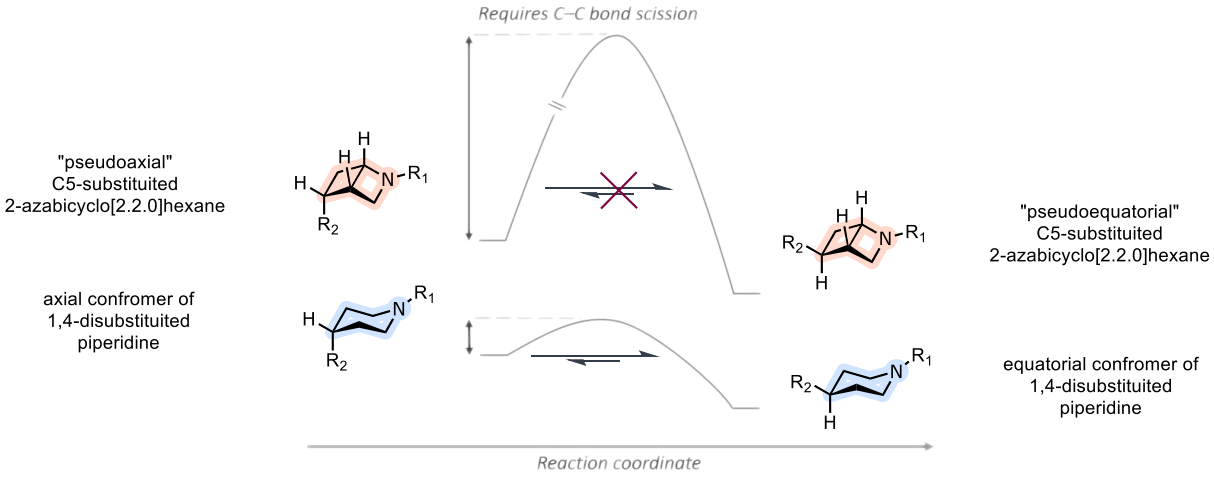


Figure 24: Energy diagrams for (hypothetical) ring flips of 1,4-disubstituted piperidines and their 2-azabicyclo[2.2.0]hexane isosteres.

A similar ring flip of the 2-azabicyclo[2.2.0]hexane scaffold would, on the other hand, require scission of the central C1–C4 carbon bond. Therefore, 2-azabicyclo[2.2.0]hexanes could be hypothetically used as programmable piperidine isosteres in special cases, where the axial conformer is preferred by the targeted receptor. By selecting appropriately substituted pyridines or carefully choreographing the sequence of transformations, we were able to install azide, amine, alcohol, bromide, carboxylic acid, hydroxymethylene, bromomethylene, and iodomethylene functional groups on the concave face of the bicycle. Additionally, electron-rich and electron-deficient 5-membered, 6-membered and fused heterocycles could be installed at the aforementioned position.

8. VARIABLE TEMPERATURE NMR STUDY

Carbamates of 2-azabicyclo[2.2.0]hex-5-enes and their saturated derivatives exhibit doubled signals in their NMR spectra due to the fact that they exist as mixtures of rotamers in solution. To prove that doubled signals are indeed a consequence of rotamerism, a variable temperature NMR study was performed on the prototypical methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**) in deuterated DMSO as a solvent. Sample temperature was determined with neat ethylene glycol sample according to the following equation:

$$T = \frac{(4.637 - \Delta)}{0.009967}$$

where Δ is the shift difference (ppm) between CH_2 & OH peaks. The results are gathered in the following table (Table 16).

Table 16: Temperature calculation for variable temperature NMR study.

Set temperature [°C]	Actual temperature [°C]
40.0	43.9
60.0	64.0
80.0	85.4

Expansions of the ^{1}H NMR spectra of **224** obtained at different temperatures are shown in the following figures (Figure 25, Figure 26). The first figure shows olefinic protons at the C5 and C6 positions. The second figure shows aliphatic protons at C1, C3 and C4 positions. NMR resonance splitting is best visible at 85 °C. At this temperature, the apparent multiplicities of olefinic proton resonances become triplets (presumably doublet of doublets with similar *J*-values). The multiplicities of the aliphatic proton resonances became triplet, doublet of quartets, and doublet, respectively (reported from low field to high field).

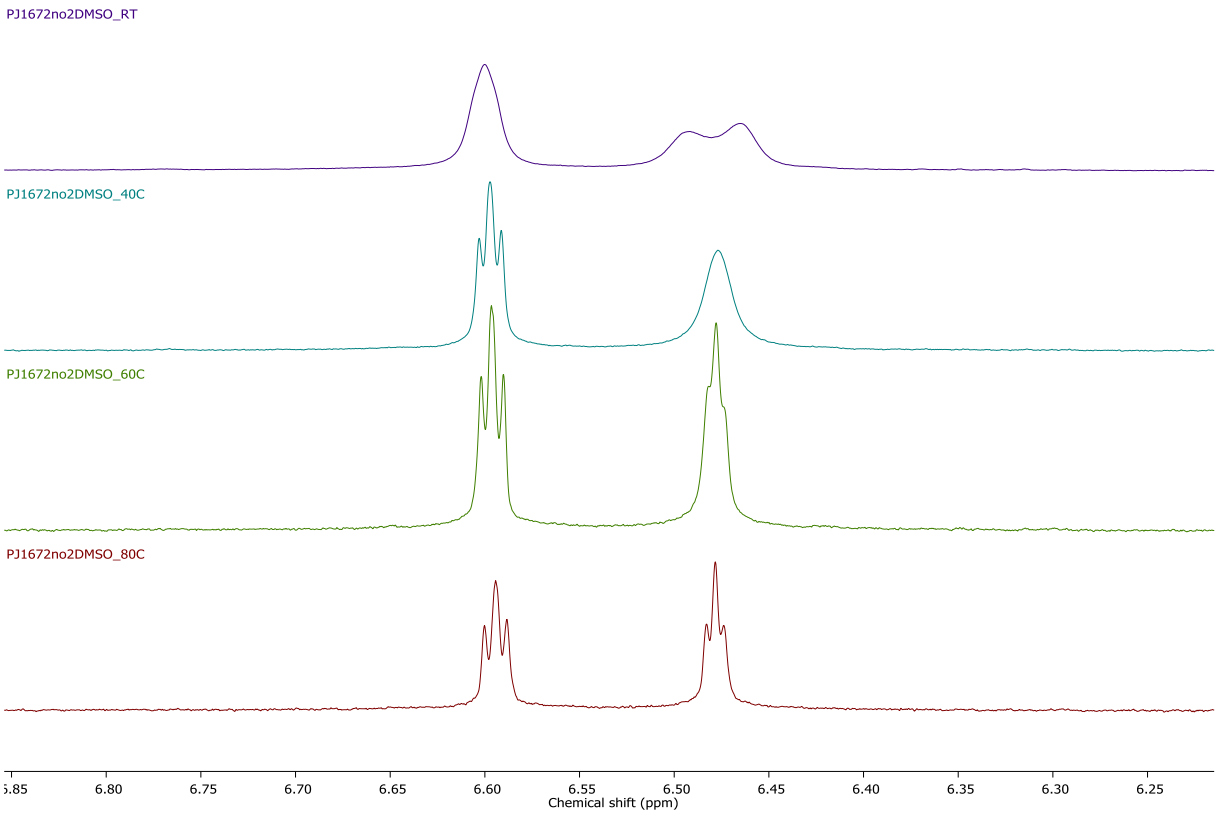


*Figure 25: ^{1}H NMR spectra of **224** at different temperatures.*

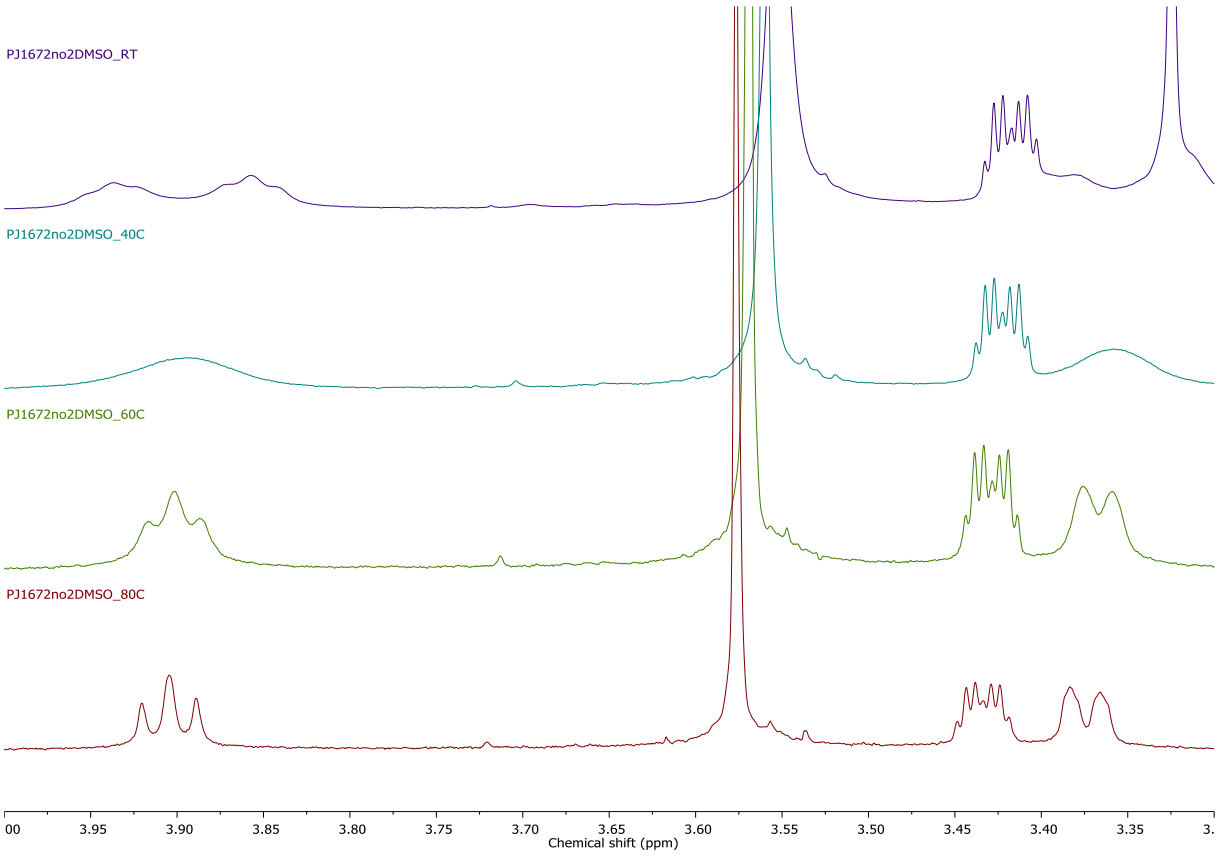


*Figure 26: ^{1}H NMR spectra of **224** at different temperatures, continued.*

9. CONCLUSIONS

Our extension of Njardarson's study from 2014 to 2023 further established the importance of the piperidine scaffold and its isosteres in medicinal chemistry. A short overview of the most commonly used piperidine isosteres is presented and their reported syntheses are outlined. It exposes several drawbacks of preparing these isosteres, such as lengthy and laborious synthetic procedures, the necessity to use precious transition metal catalysts, limited possibilities for introduction of functional groups for further elaboration, and poor atom economy. As a workaround to these issues, we evaluated the potential of 2-azabicyclo[2.2.0]hexane scaffold to serve as a malleable, easily accessible and programmable piperidine isostere. EVA was performed to compare the overlap between 1,4-disubstituted piperidines and their isosteres as well as to compare piperidine isosteres among themselves.

The substrate scope of the dearomatization / 4π-electrocyclization sequence was expanded considerably, allowing us to use commercially available pyridines to yield 2-azabicyclo[2.2.0]hex-5-enes with functional groups already attached. These include synthetically tractable vinyl bromide, vinyl enol ether, enimide and hydroxymethylene moieties. Two disubstituted pyridines were also amenable to the dearomatization / 4π-electrocyclization sequence and gave rise to the corresponding disubstituted 2-azabicyclo[2.2.0]hex-5-enes. By performing at least one of the two steps in a flow chemistry setting, the improvement of overall yields will be attempted in our future studies.

The promiscuity of modern olefin chemistry was challenged against the strained olefin of the 2-azabicyclo[2.2.0]hex-5-ene system and several formal hydrofunctionalizations were performed. These include rhodium-catalyzed hydroboration, palladium-catalyzed hydroarylation, iron-catalyzed hydroazidation, and reductive olefin coupling. The products of classic olefin transformations like hydrogenation, epoxidation, and aziridination were isolated and fully characterized. Skeletal editing via hydrogenation of the epoxide and aziridine products gave us straightforward access to 3-oxa-6-azabicyclo[3.2.0]heptane and 3,6-diazabicyclo[3.2.0]heptane systems.

2-azabicyclo[2.2.0]hex-5-enes and their "hydrofunctionalization" products were further elaborated by performing dual photo/nickel catalyzed cross-coupling, Ullmann coupling, and Suzuki-Miyaura coupling. It was demonstrated that various carbamate protecting groups could be removed, revealing free amines, which could be transformed into various amides or alkylamines. By performing redox manipulations and functional group interconversions, 2-azabicyclo[2.2.0]hexanes with carboxylic acid, amine, alcohol, halide and ketone moieties were synthesized.

A general blueprint of currently accessible functionality at each of the 9 positions of the 2-azabicyclo[2.2.0]hexane scaffold was devised and then employed for making drug (Thioridazine & Moperone) and lead compound isosteres. Biological assays and stability studies of these compounds are currently ongoing in our laboratories.

10. EXPERIMENTAL SECTION

All chemicals were purchased from commercial suppliers (Sigma, Alfa, Acros, Merck, Oakwood, Ambeed, TCI, Fluorochem, BLD, AA Blocks, etc.) and used as received, unless otherwise noted. 4-bromonicotinaldehyde **272** was prepared according to literature procedure[132], with a slight modification of using 4-bromopyridine hydrochloride and 2.5 eq. LDA instead of 4-bromopyridne. (3-bromo-pyridin-4-yl)-methanol **273** was prepared according to literature procedure.[133] 4-bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine **274** was prepared according to literature procedure[134], with a slight modification of using DCM instead of DMF.

Diethyl ether (ACS grade), dichloromethane (ACS grade), tetrahydrofuran (HPLC grade), acetonitrile (HPLC grade), and toluene (ACS grade) were dried for reactions using the MB-SPS solvent purification system containing activated alumina manufactured by MBRAUN. Reaction temperatures correspond to the external temperature of the reaction vessel unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} glass sheets. Visualization was accomplished with UV light, cerium molybdate and/or potassium permanganate ($KMnO_4$). Retention factor (R_f) values reported were measured in triplicate using 10 × 2 cm TLC plates in a developing chamber containing the solvent system described. Silicycle SiliaFlash® P60 (SiO_2, 40–63 µm particle size, 230–400 mesh), aluminum oxide activated, basic, Brockmann I (Al_2O_3, ~60 Mesh) or aluminum oxide 90, neutral, were used for flash column chromatography. Alternatively, compounds were purified using Biotage® Isolera™ One (AQ C18 column spherical; 20 – 35 µm; 100 Å) or at Merck separation facilities.

^{1}H NMR spectra were obtained at 400 MHz, 500 MHz or 600 MHz. ^{13}C NMR were obtained at 100 MHz, 126 MHz or 151 MHz. ^{19}F NMR spectra were obtained at 471 MHz or 565 MHz. ^{11}B NMR spectra were obtained at 160 MHz or 193 MHz. NMR spectra were recorded using a Bruker Avance III 400 MHz spectrometer, a Bruker CAB AV4 500 MHz spectrometer equipped with wide-band BBO probe, a Bruker Avance III 500 MHz spectrometer equipped with BB CryoProbe or a Bruker NEO NMR 600 MHz spectrometer equipped with BBO prodigy probe and were referenced to residual chloroform (7.26 ppm, ^{1}H), residual DMSO (2.50 ppm, ^{1}H), solvent chloroform-*d* (77.16 ppm, ^{13}C), solvent DMSO-d_6 (39.52 ppm, ^{13}C) or internal $PhCF_3$ (–62.61 ppm, ^{19}F). Chemical shifts are reported in parts per million (ppm) and multiplicities are indicated as: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in hertz.

Mass spectrometry (MS) was performed at the University of Illinois Mass Spectrometry Laboratory. Electrospray ionization (ESI+) spectra were performed using Waters Synapt G2-Si time-of flight (TOF) mass analyzer. Data is reported in the form of m/z. Infrared (IR) spectra of neat samples were measured on a Perkin-Elmer Spectrum Two FT-IR ATR spectrometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0 – 33% T); m (medium, 34 – 66% T), w (weak, 67 – 100% T), and br (broad). Photochemical reactions were performed in Pyrex or quartz reaction vessels placed in the center of a Rayonet RPR-100 photochemical reactor equipped with 12 G8T5E UV lamps (310 nm) or 16 F8T5BL UV lamps (350 nm) (Figure 27).

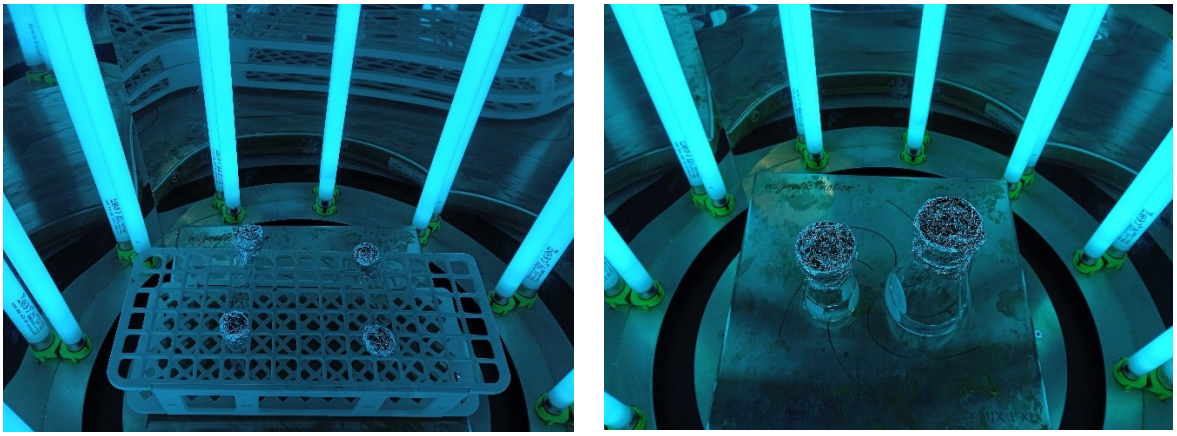


Figure 27: Photochemical set-up for small scale (left) and large scale (right) 4π-electrocyclizations.

Computational studies

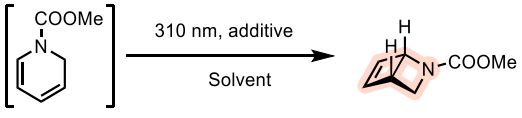
The structures were parsed from ChemDraw CDXML files using in-house scripts. Explicit hydrogen atoms were added, and the structures were subjected to MMFF94 forcefield minimization, as implemented in OpenBabel 3.1.0.[135] Obtained structures were subjected to CREST[136]/GFNFF[137] conformer generation with the iMTD-GC[138] workflow. The conformers were subjected to DFT minimization as obtained. Some of the conformers converged to the same structure after DFT optimization and the duplicate structures were discarded.

All DFT calculations were performed with ORCA 5.0.3 release version.[139–141] RKS B3LYP/def2-TZVP with the following input:

```
!rks b3lyp def2-tzvp opt freq tightopt tightscf noprintmos miniprint
```

The stationary state nature of the structures reported was verified by absence of imaginary frequencies in the diagonalized Hessian matrix obtained by analytical frequency calculations. Boltzmann weights were calculated with the Gibbs function values using unscaled ZPVE contributions and ideal gas finite temperature corrections at 298.15K and 1 atm pressure.

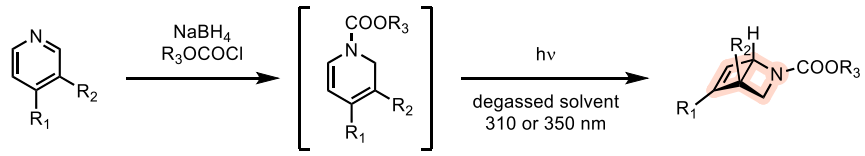
General procedure for optimization of 4π-electrocyclization



223 **224**

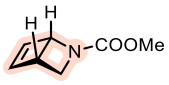
A tall quartz culture tube was charged with crude 1,2-dihydropyridine **223** (13.9 mg, 0.1 mmol, 1.0 eq.), additive and the specified amount of solvent. The resulting solution was degassed by sparging with argon for 2 minutes in an ultrasonic bath and then irradiated in a Rayonet photoreactor equipped with 310 nm lamps for 24 hours. Solvent was removed and internal standard 1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol, 1.0 eq.) was added. The resulting mixture was dissolved in $CDCl_3$ (0.7 mL) and transferred into an NMR tube. The reaction yield was determined by integrating product and internal standard signals.

General procedure for preparation of 2-azabicyclo[2.2.0]hex-5-enes



Following a slightly modified procedure[73], a flame dried two-neck round bottom flask was charged with (substituted) pyridine, $NaBH_4$ and anhydrous Et_2O (or DCM) under nitrogen atmosphere. Reaction mixture was cooled to -78 °C in an acetone/dry ice cooling bath and MeOH was added slowly. The chloroformate of choice was then added dropwise to the resulting suspension, which was either stirred at -78 °C or left to warm up to the final temperature. Afterwards, the reaction mixture was diluted with Et_2O and quenched with water. The organic phase was separated from the aqueous phase, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Crude product was purified by passing through a short plug of basic alumina (activated, Brockmann I) with Et_2O to yield the corresponding 1,2-dihydropyridine. Its solution in an appropriate solvent was first degassed by sparging with argon for 2–3 minutes in an ultrasonic bath and then irradiated in a quartz culture tube inside a Rayonet photoreactor. The solvent was removed, and crude 2-azabicyclo[2.2.0]hex-5-ene was directly loaded onto a column. Gradient elution afforded the desired product.

Synthesis of methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224)**



224

Following the general procedure, pyridine was dearomatized in 69% yield. After irradiation, methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 2.13 g, 58%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 30) as a slightly yellow clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
40 mmol	1.0 eq.	1.0 eq.	15 mL	5 mL	-78 °C, 2 h	EtOAc, 0.5 M, 310 nm, 6 d

^{1}H NMR (600 MHz, $CDCl_3$, 296 K, rotamers) δ 6.61 – 6.35 (m, 2H), 4.81 (m, 1H), 3.94 (bs, 1H), 3.66 (s, 3H), 3.48 (d, *J* = 8.5 Hz, 1H), 3.40 (d, *J* = 6.1 Hz, 1H).

^{1}H NMR (499 MHz, DMSO-d_6, 358K) δ 6.59 (t, *J* = 3.0 Hz, 1H), 6.48 (t, *J* = 2.4 Hz, 1H), 4.77 (td, *J* = 3.2, 1.4 Hz, 1H), 3.90 (t, *J* = 7.9 Hz, 1H), 3.58 (s, 3H), 3.43 (dq, *J* = 7.7, 2.8 Hz, 1H), 3.37 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$, rotamers, RT) δ 157.8, 143.4, 143.2, 140.9, 140.5, 65.8, 65.3, 52.3, 50.2, 49.4, 38.4.

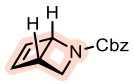
R_f = 0.37 (hexanes : EtOAc = 3 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2955 (w), 1706 (s), 1448 (s), 1368 (s), 1195 (m), 1154 (m), 1112 (m), 761 (w).

HRMS (ESI-TOF) calculated for $C_7H_9NO_2$+H^+: 140.0712, found: 140.0711.

Spectral data matches previously reported values.[74]

Synthesis of benzyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**259)**



259

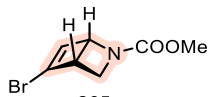
Following the general procedure, pyridine was dearomatized in 77% yield. After irradiation, benzyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**259**, 1.60 g, 32%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 20 ⟶ 100 : 30) as a slightly yellow clear oil.

Scale	CbzCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
30 mmol	1.1 eq.	1.2 eq.	15 mL	5 mL	-78 °C ⟶ -20°C	EtOAc, 0.5 M, 310 nm, 7 d

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.35 (m, 5H), 6.61 – 6.36 (m, 2H), 5.11 (m, 2H), 4.86 (m, 1H), 3.98 (m, 1H), 3.54 – 3.50 (m, 1H), 3.41 (m, 1H).

Spectral data matches previously reported values.[74]

Synthesis of methyl 5-bromo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**265**)



265

Following the general procedure, 4-bromopyridinium chloride was dearomatized in 69% yield. After irradiation, methyl 5-bromo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**265**, 0.337 g, 46%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 20) as a slightly yellow clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation (pyrex glassware)
5 mmol	1.1 eq.	2.2 eq.	15 mL	5 mL	-78 °C ⟶ -5°C	Me_2CO, 0.07 M, 350 nm, 7 d

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 6.58 (m, 1H), 4.84 (bs, 1H), 3.89 (bs, 1H), 3.64 (s, 3H), 3.60 (m, 1H), 3.52 (m, 1H).

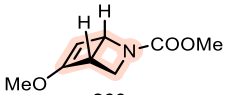
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 157.6, 157.5, 140.7, 140.3, 127.0, 126.6, 63.9, 63.4, 52.5, 49.2, 48.4, 44.9.

R_f = 0.62 (hexanes : EtOAc = 3 : 2; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2887 (w), 1702 (s), 1555 (w), 1445 (s), 1360 (s), 1261 (w), 1199 (m), 1154 (m), 972 (w), 921 (w).

HRMS (ESI-TOF) calculated for $C_7H_8NO_2Br+H^+$: 217.9817, found: 217.9817.

Synthesis of methyl 5-methoxy-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**266**)



266

Following the reported procedure[142], 4-methoxypyridine was dearomatized in 81% yield. After irradiation, methyl 5-methoxy-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**266**, 2.4 g, 71%) was isolated via filtration (basic Al_2O_3, Et_2O) as a slightly yellow clear oil. Further purification by gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 20 on a neutral alumina column afforded analytically pure sample.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
18 mmol	1.3 eq.	1.3 eq.	40 mL	6 mL	-78 °C, 15 min	Me_2CO, 0.25 M, 310 nm, 48 h

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 5.12 (m, 1H), 4.56 (m, 1H), 3.84 (bs, 1H), 3.65 (bs, 6H), 3.56 (m, 1H), 3.41 (dq, *J* = 5.4, 2.7 Hz, 1H).

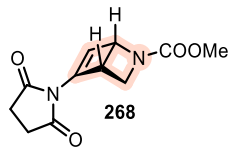
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 160.9, 160.7, 158.0, 101.8, 101.5, 57.3, 56.6, 56.3, 52.3, 48.4, 47.6, 39.0.

R_f = 0.40 (hexanes : EtOAc = 4 : 1; $KMnO_4$, alumina)

IR (KBr discs, cm^{-1}): 2956 (w), 1705 (s), 1614 (s), 1447 (m), 1370 (m), 1339 (s), 1227 (w), 1154 (w), 769 (w).

HRMS (ESI-TOF) calculated for $C_8H_{11}NO_3$+H^+: 170.0817, found 170.0816.

Synthesis of methyl 5-(2,5-dioxopyrrolidin-1-yl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**268**)



268

Following the general procedure, 1-(pyridin-4-yl)pyrrolidine-2,5-dione was dearomatized in 76% yield. After irradiation, methyl 5-(2,5-dioxopyrrolidin-1-yl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**268**, 130.2 mg, 74%) was isolated via flash column chromatography (SiO_2, EtOAc) as a colorless clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	DCM	*T, t*	Irradiation
0.9 mmol	1.1 eq.	1.1 eq.	3 mL	6 mL	-78 °C ⟶ 0 °C	DCM, 0.1 M, 310 nm, 26 h

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 6.32 (m, 1H), 4.80 (m, 1H), 4.00 (bs, 1H), 3.94 (bs, 1H), 3.70 – 3.56 (m, 4H), 2.76 (s, 4H).

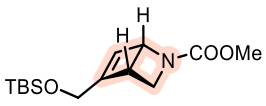
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 174.6, 157.7, 157.6, 137.5, 122.3, 121.8, 63.4, 62.7, 52.4, 49.6, 48.8, 39.5, 28.4.

R_f = 0.45 (EtOAc; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2956 (m), 2890(w), 1711 (s), 1698 (s), 1608 (m), 1448 (m), 1362 (s), 1173 (s), 1139 (m).

HRMS (ESI-TOF) calculated for $C_{11}H_{12}N_2O_4$+H^+: 237.0875, found 237.0876.

Synthesis of methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**269**)



269

Following the general procedure, 4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine was dearomatized in 81% yield. After irradiation, methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**269**, 2.0 g, 74%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 20) as a slightly yellow clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
8.8 mmol	1.1 eq.	1.1 eq.	6 mL	2 mL	-78 °C ⟶ -5°C	Me_2CO, 0.1 M, 310 nm, 7 d

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.32 (m, 1H), 4.70 (m, 1H), 4.67 (s), 4.22 (m, 2H), 3.91 (m, 1H), 3.65 (broad s, 3H), 3.50 (m, 1H), 3.34 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H).

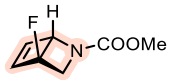
^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.8, 155.9, 155.7, 132.3, 131.9, 62.3, 61.7, 60.2, 52.30, 49.7, 48.8, 37.0, 25.9, 18.5, -5.3, -5.3.

R_f = 0.44 (hexanes : EtOAc = 4 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2955 (m), 2930 (w), 2886 (w), 2857 (w), 1712 (s), 1447 (m), 1363 (m), 1094 (m), 838 (s), 776 (m).

HRMS (ESI-TOF) calculated for $C_{14}H_{25}NO_3Si+H^+$: 284.1682, found 284.1671.

Synthesis of methyl 4-fluoro-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**260**)



260

Following the general procedure, 4-fluoropyridine was dearomatized in 50% yield. After irradiation, methyl 4-fluoro-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**260**, 0.172 g, 13%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 30) as a slightly yellow clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
17.6 mmol	1.2 eq.	1.1 eq.	6 mL	2 mL	-78 °C, 2 h	Me_2CO, 0.2 M, 310 nm, 24 h

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 6.50 (q, *J* = 2.4 Hz, 2H), 5.00 (bs, 1H), 4.15 (dd, *J* = 16.5, 9.7 Hz, 1H), 3.88 (t, *J* = 9.2 Hz, 1H), 3.67 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.7, 156.7, 140.2, 140.0, 138.6, 93.2, 91.1, 72.2, 55.8, 52.7.

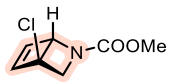
^{19}F NMR (471 MHz, $CDCl_3$) δ -159.9.

R_f = 0.53 (hexanes : EtOAc = 2 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2955 (w), 1708 (s), 1448 (s), 1368 (s), 1315 (w) 1223 (w), 1195 (w), 1156 (w), 1117 (w), 1070 (w), 785 (w).

HRMS (ESI-TOF) calculated for $C_7H_8NO_2F+H^+$: 158.0617, found: 158.0617.

Synthesis of methyl 4-chloro-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**261**)



261

Following the general procedure, 3-chloropyridine was dearomatized in 60% yield. After irradiation, methyl 4-chloro-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**261**, 48 mg, 9%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 25) as a slightly yellow clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
4.9 mmol	1.0 eq.	1.1 eq.	3 mL	1 mL	-78 °C, 1.5 h	Me_2CO, 0.06 M, 350 nm, 7 d

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 6.48 (m, 2H), 4.89 (bs, 1H), 4.12 (d, *J* = 9.3 Hz, 1H), 4.00 (d, *J* = 9.3 Hz, 1H), 3.68 (s, 3H).

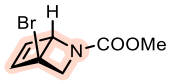
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 156.8, 143.3, 138.4, 138.1, 72.8, 72.4, 61.2, 60.0, 59.3, 52.7.

R_f = 0.74 (hexanes : EtOAc = 2 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2955 (w), 2885 (w), 1712 (s), 1447 (s), 1367 (s), 1291 (w), 1152 (m), 1105 (m), 783 (w), 769 (w).

HRMS (ESI-TOF) calculated for $C_7H_8NO_2Cl+H^+$: 174.0322, found: 174.0322.

Synthesis of methyl 4-bromo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**262**)



262

Following the general procedure, 3-bromopyridine was dearomatized in 67% yield. After irradiation, methyl 4-bromo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**262**, 0.229 g, 17%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 20) as a slightly yellow clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
9.6 mmol	1.1 eq.	1.1 eq.	7.5 mL	2.5 mL	-78 °C, 1 h	Me_2CO, 0.13 M, 350 nm, 7 d

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 6.52 (s, 2H), 4.96 (s, 1H), 4.24 (d, *J* = 9.5 Hz, 1H), 4.09 (d, *J* = 9.5 Hz, 1H), 3.68 (s, 3H).

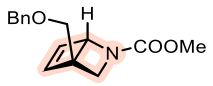
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 156.8, 144.4, 138.4, 138.0, 73.0, 72.7, 60.9, 60.3, 52.7, 49.4.

R_f = 0.51 (hexanes : EtOAc = 3 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2884 (w), 1710 (s), 1446 (s), 1362 (s), 1286 (w), 1147 (m), 1107 (m), 782 (w), 768 (w).

HRMS (ESI-TOF) calculated for $C_7H_8NO_2Br+H^+$: 217.9817, found: 217.911.

Synthesis of methyl 4-((benzyloxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**263**)



263

Following the general procedure, 3-((benzyloxy)methyl)pyridine was dearomatized in 69% yield. After irradiation, methyl 4-((benzyloxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**263**, 0.173 g, 18%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 30) as a slightly yellow clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
15 mmol	1.1 eq.	1.1 eq.	6 mL	2 mL	-78 °C ⟶ -20°C	Me_2CO, 0.2 M, 310 nm, 36 h

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.38 – 7.27 (m, 5H), 6.57 – 6.36 (m, 2H), 4.73 – 4.57 (m, 1H), 4.55 (s, 2H), 3.89 (d, *J* = 8.6 Hz, 1H), 3.67 (s, 3H), 3.62 (d, *J* = 3.4 Hz, 2H), 3.54 (dd, *J* = 8.6, 1.5 Hz, 1H).

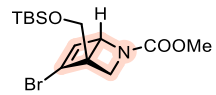
^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.6, 143.7, 139.6, 139.05, 138.1, 128.6, 127.9, 127.7, 73.4, 69.39, 66.3, 65.7, 52.4, 51.9, 51.1, 49.8.

R_f = 0.74 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2952 (w), 2879 (w), 2858 (w), 1704 (s), 1449 (m), 1359 (m), 1085 (m), 783 (w), 765 (w), 738 (w), 699 (w).

HRMS (ESI-TOF) calculated for $C_{15}H_{17}NO_3$+Na^+: 282.1101, found: 282.1098.

Synthesis of methyl 5-bromo-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**270**)



270

Following the general procedure, 4-bromo-3-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine was dearomatized in 92% yield. After irradiation, methyl 5-bromo-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**270**, 0.374 g, 35%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 30) as a slightly yellow clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
3.2 mmol	1.1 eq.	1.1 eq.	6 mL	2 mL	-78 °C ⟶ -10°C	Me_2CO, 0.2 M, 310 nm, 41 h

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 6.58 (m, 1H), 4.72 (m, 1H), 3.78 (m, 3H), 3.67 (s, 3H), 3.50 (m, 1H), 0.87 (s, 9H), 0.05 (s, 6H).

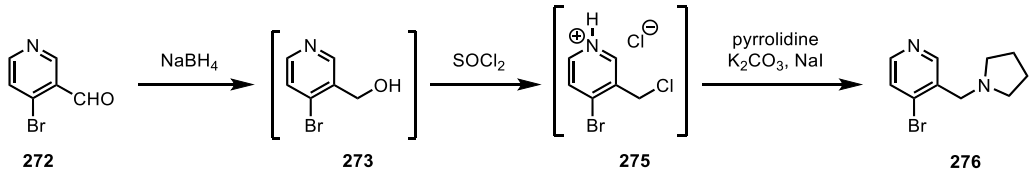
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 157.6, 138.9, 138.4, 128.1, 127.8, 64.9, 64.4, 60.5, 56.4, 52.5, 49.5, 48.8, 25.9, 18.3, -5.3, -5.3.

R_f = 0.34 (hexanes : EtOAc = 5 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2954 (m), 2930 (m), 2885 (w), 2857 (m), 1716 (s), 1558 (w), 1447 (s), 1364 (s), 1111 (m), 838 (s), 777 (m).

HRMS (ESI-TOF) calculated for $C_{14}H_{24}NO_3BrSi$+H^+: 362.0787, found 362.0783.

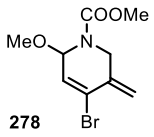
Synthesis of 4-bromo-3-(pyrrolidin-1-ylmethyl)pyridine (**276**)



4-bromonicotinaldehyde **272** (1.324 g, 7.12 mmol) was dissolved in MeOH (36 mL) and the resulting solution was cooled to 0 °C. Small portions of $NaBH_4$ were added until TLC analysis indicated complete consumption of starting material. The reaction mixture was then quenched with 10% aqueous NH_4Cl and extracted with EtOAc (3 x 100 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude alcohol **273** was dissolved in DCM (28 mL) and $SOCl_2$ (1.25 mL, 1.640 g/mL, 17.1) was added in one portion. After 30 minutes of stirring at room temperature, the resulting suspension was filtered, and the solid residue was washed with Et_2O. Filtration and washing with Et_2O were repeated until more product crashed out of the filtrate. The combined solid chloride **275** was suspended in MeCN (28 mL) and NaI (1.279 g, 8.5 mmol), K_2CO_3 (3.146 g, 22.8 mmol) and pyrrolidine (940 μL, 0.866 g/mL, 11.4 mmol) were added sequentially in one portion. The resulting suspension was stirred vigorously overnight and then partitioned between 100 mL of EtOAc and 100 mL of water. The organic phase was separated, and the aqueous phase extracted two more times with the same amount of EtOAc. Combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield 4-bromo-3-(pyrrolidin-1-ylmethyl)pyridine (**276**, 0.837 g, 3.47 mmol, 49% over 3 steps) as a viscous brown oil. The resulting product could be further purified by flash column chromatography (SiO_2, DCM : MeOH = 100 : 2 ⟶ 100 : 10 (+1% saturated aqueous NH_3)).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.27 (d, *J* = 5.3 Hz, 1H), 7.48 (d, *J* = 5.2 Hz, 1H), 3.76 (s, 2H), 2.61 (bs, 4H), 1.81 (bs, 4H).

Methyl 4-bromo-6-methoxy-3-methylene-3,6-dihydropyridine-1(2H)-carboxylate (**278**)



278

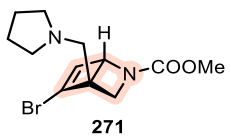
The title compound formed during reductive dearomatization of 4-bromo-3-(pyrrolidin-1-ylmethyl)pyridine (**278**) if the temperature was not rigorously controlled.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 6.30 (m, 1H), 5.68 – 5.37 (m, 2H), 5.26 (m, 1H), 4.69 (m, 1H), 4.05 – 3.87 (m, 1H), 3.74 (s, 3H), 3.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 155.9, 155.4, 136.4, 136.3, 129.0, 128.4, 125.2, 124.6, 118.1, 117.5, 81.4, 56.0, 55.6, 53.16, 43.1, 42.8.

HRMS (ESI-TOF) calculated for $C_9H_{13}NO_3Br+H^+$-MeOH: 229.9817, found: 229.9818.

Synthesis of methyl 5-bromo-4-(pyrrolidin-1-ylmethyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**271**)



271

Following the general procedure, 4-bromo-3-(pyrrolidin-1-ylmethyl)pyridine was dearomatized in 88% yield. After irradiation, methyl 5-bromo-4-(pyrrolidin-1-ylmethyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**271**, 49.5 mg, 24%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 100 ⟶ pure EtOAc (+1% Et_3N)) as a colorless clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
0.8 mmol	3.5 eq.	3.5 eq.	2.1 mL	0.7 mL	-78 °C ⟶ -15°C	Me_2CO, 0.1 M, 310 nm, 49 h

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 6.56 (m, 1H), 4.73 (m, 1H), 3.92 (m, 2H), 3.67 (s, 3H), 3.47 (bs, 1H), 2.90 (d, *J* = 13.7 Hz, 1H), 2.72 – 2.44 (m, 4H), 1.76 (m, 4H).

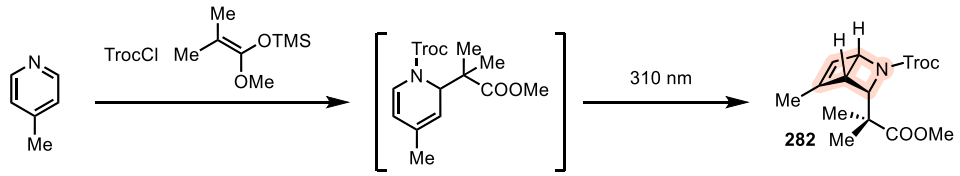
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 157.8, 157.6, 138.2, 137.8, 123.0, 129.5, 66.7, 66.2, 55.9, 55.15, 54.8, 52.6, 50.6, 49.9, 23.8.

R_f = 0.41 (EtOAc; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2955 (m), 2909 (w), 2879 (w), 2791 (m), 1712 (s), 1558 (w), 1446 (s), 1364 (s), 1212 (m), 1154 (w), 915 (w).

HRMS (ESI-TOF) calculated for $C_{12}H_{17}N_2O_3Br+H^+$: 301.0552, found 301.0555.

Synthesis of 2,2,2-trichloroethyl 3-(1-methoxy-2-methyl-1-oxopropan-2-yl)-5-methyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**282**)



282

A flame dried 100 mL two neck round bottom flask was charged with 4-methylpyridine (240 μL, 0.957 g/mL, 2.47 mmol, 1.0 eq.) and anhydrous DCM (25 mL, 0.1 M) under nitrogen atmosphere. The resulting solution was cooled to -78°C in an acetone/dry ice bath. TrocCl (350 μL, 1.539 g/mL, 2.54 mmol, 1.0 eq.) was added dropwise via syringe. Methyl trimethylsilyl dimethylketene acetal (1.0 mL, 0.858 g/mL, 5.0 mmol, 2.0 eq.) was then added in one portion via syringe. The resulting mixture was left to warm up slowly to room temperature overnight (cooling bath was not removed). Solvent was removed under reduced pressure and the residue directly loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 1 ⟶ 100 : 3 afforded the corresponding 1,2-dihydropyridine (0.329 g, 0.886 mmol, 36%) as a colorless clear oil.

DCM solution (3.5 mL, 0.14 M) of the crude 1,2-dihydropyridine (261.2 mg, 0.705 mmol) in a quartz test tube was degassed by sparging with argon for 3 minutes in an ultrasonic bath. Degassed solution was then irradiated in a Rayonet photoreactor equipped with 310 nm lamps overnight. Solvent was removed and crude product was directly loaded onto a column. Gradient elution with hexanes : Et_2O = 100 : 5 ⟶ 100 : 30 afforded 2,2,2-trichloroethyl 3-(1-methoxy-2-methyl-1-oxopropan-2-yl)-5-

methyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**282**, 95.7 mg, 0.285 mmol, 37%) as a slightly yellow clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 6.14 (bs, 1H), 4.75 (m, 1H), 4.70 (s, 1H), 4.68 – 4.54 (m, 2H), 3.70 (s, 3H), 3.46 (d, *J* = 7.0 Hz, 1H), 1.80 (s, 3H), 1.36 (s, 3H), 1.22 (s, 3H).

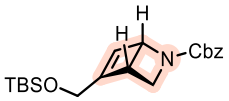
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 177.2, 153.8, 151.1, 134.2, 96.1, 74.3, 65.2, 59.38, 52.1, 44.7, 44.4, 24.1, 22.2, 17.5.

R_f = 0.64 (hexanes : EtOAc = 4 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2987 (w), 2950 (w), 2916 (w), 1720 (s), 1617 (w), 1391 (m), 1340 (m), 1274 (m), 1123 (s), 819 (w), 714 (w).

HRMS (ESI-TOF) calculated for $C_{14}H_{18}NO_4Cl_3+H^+$: 370.0380, found: 370.0375.

Synthesis of benzyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**295**)



295

Following the general procedure, 4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine was dearomatized in 88% yield. After irradiation, benzyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**295**, 0.291 g, 31%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 40) as a slightly yellow clear oil.

Scale	CbzCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
3.3 mmol	1.1 eq.	1.1 eq.	3 mL	1 mL	-78 °C ⟶ -10°C	Me_2CO, 0.18 M, 310 nm, 36 h

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.38 – 7.27 (m, 5H), 6.33 (m, 1H), 5.16 – 5.02 (m, 1H), 4.75 (m, 1H), 4.23 (m, 2H), 4.01 – 3.89 (m, 1H), 3.55 (d, *J* = 8.7 Hz, 1H), 3.35 (dd, *J* = 6.9, 2.7 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 6H).

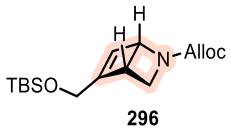
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 157.2, 155.9, 155.7, 136.9, 132.3, 131.9, 128.5, 128.04, 128.0, 66.6, 62.4, 61.8, 60.2, 60.1, 49.7, 49.0, 37.0, 25.9, 18.5.

R_f = 0.24 (hexanes : EtOAc = 10 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2929 (w), 2887 (w), 2856 (w), 1705 (s), 1401 (m), 1345 (m), 1138 (w), 1091 (s), 835 (s), 775 (m), 731 (w), 697 (w).

HRMS (ESI-TOF) calculated for $C_{20}H_{29}NO_3Si+H^+$: 360.1995, found: 360.1995.

Synthesis of allyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**296**)



296

Following the general procedure, 4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine was dearomatized in 89% yield. After irradiation, allyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**296**, 0.211 g, 43%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 40) as a slightly yellow clear oil.

Scale	AllocCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
1.8 mmol	1.1 eq.	1.1 eq.	3 mL	1 mL	-78 °C ⟶ -10°C	Me_2CO, 0.1 M, 310 nm, 36 h

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 6.34 (m, 1H), 5.91 (m, 1H), 5.28 (m, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 4.73 (m, 1H), 4.55 (s, 2H), 4.29 – 4.13 (m, 2H), 4.06 – 3.86 (m, 1H), 3.52 (s, 1H), 3.43 – 3.32 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H).

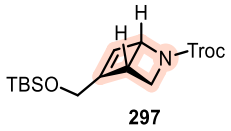
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 157.0, 156.0, 155.7, 133.2, 132.4, 131.9, 117.5, 65.6, 62.3, 61.7, 60.3, 60.2, 49.7, 48.9, 37.0, 25.9, 18.5, -5.3, -5.3.

R_f = 0.30 (hexanes : EtOAc = 10 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2888 (w), 2857 (w), 1711 (s), 1398 (m), 1337 (m), 1257 (w), 1140 (m), 1093 (s), 838 (s), 776 (w).

HRMS (ESI-TOF) calculated for $C_{16}H_{27}NO_3Si+H^+$: 310.1838, found: 310.1833.

Synthesis of 2,2,2-trichloroethyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**297**)



297

Following the general procedure, 4-(((*tert*-butyldimethylsilyl)oxy)methyl)pyridine was dearomatized in 86% yield. After irradiation, 2,2,2-trichloroethyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**297**, 0.143 g, 14%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 10 ⟶ 100 : 40) as a slightly yellow clear oil.

Scale	TrocCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
3 mmol	1.1 eq.	1.1 eq.	3 mL	1 mL	-78 °C ⟶ -10°C	Me_2CO, 0.17 M, 310 nm, 36 h

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (m, 1H), 4.85 – 4.56 (m, 3H), 4.30 – 4.17 (m, 2H), 4.01 (m, 1H), 3.60 (m, 1H), 3.40 (dd, *J* = 6.8, 2.6 Hz, 1H), 0.89 (s, 6H), 0.06 (s, 4H).

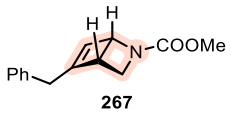
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.1, 155.1, 155.0, 132.1, 132.0, 95.8, 74.6, 74.5, 62.7, 62.0, 60.2, 60.1, 49.9, 49.2, 37.3, 37.2, 25.9, 18.5, -5.2, -5.3.

R_f = 0.36 (hexanes : EtOAc = 10 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2930 (w), 2887 (w), 2857 (w), 1723 (s), 1399 (m), 1139 (w), 1117 (m), 1097 (w), 836 (s), 776 (m), 717 (w).

HRMS (ESI-TOF) calculated for $C_{15}H_{24}NO_3Cl_3Si+H^+$: 400.0669, found: 400.0660.

Synthesis of methyl 5-benzyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**267**)



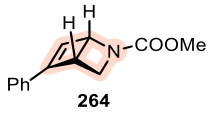
267

Following the general procedure, 4-benzylpyridine was dearomatized in 85% yield. After irradiation, methyl 5-benzyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**267**, 0.600 g, 77%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 25 ⟶ 100 : 50) as a slightly yellow clear oil.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
4 mmol	1.1 eq.	1.1 eq.	6 mL	2 mL	-78 °C ⟶ -5°C	EtOAc, 0.17 M, 310 nm, 25 h

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.34 – 7.17 (m, 5H), 6.29 – 6.05 (m, 1H), 4.78 – 4.59 (m, 1H), 3.89 – 3.79 (m, 1H), 3.65 (s, 3H), 3.47 (s, 2H), 3.38 – 3.25 (m, 2H).

Synthesis of methyl 5-phenyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**264**)



264

Following the general procedure, 4-phenylpyridine was dearomatized in 92% yield. After irradiation, methyl 5-phenyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**264**, 0.182 g, 35%) was isolated via flash column chromatography (SiO_2, hexanes : EtOAc = 100 : 20 ⟶ 100 : 40) as a slightly yellow liquid that solidified upon storage in freezer.

Scale	MeOCOCl	$NaBH_4$	MeOH	Et_2O	*T, t*	Irradiation
3 mmol	1.1 eq.	1.1 eq.	5 mL	10 mL	-78 °C ⟶ 5°C	EtOAc, 0.08 M, 310 nm, 41 h

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 5H), 6.70 (m, 1H), 4.86 (m, 1H), 4.08 (t, *J* = 7.0 Hz, 1H), 3.79 – 3.62 (m, 4H), 3.57 (d, *J* = 8.5 Hz, 1H).

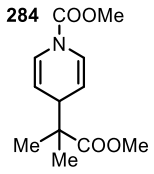
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 157.9, 153.0, 152.8, 132.7, 129.8, 129.3, 129.1, 128.75, 125.3, 61.6, 61.0, 52.4, 50.1, 49.3, 36.5.

R_f = 0.39 (hexanes : Et_2O = 1 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 3056 (w), 2953 (w), 2884 (w), 1704 (s), 1447 (s), 1364(s), 1114 (m), 759 (w), 693 (w).

HRMS (ESI-TOF) calculated for $C_{13}H_{13}NO_2+H^+$: 216.1025, found: 216.1024.

Methyl 4-(1-methoxy-2-methyl-1-oxopropan-2-yl)pyridine-1(4H)-carboxylate (**284**)

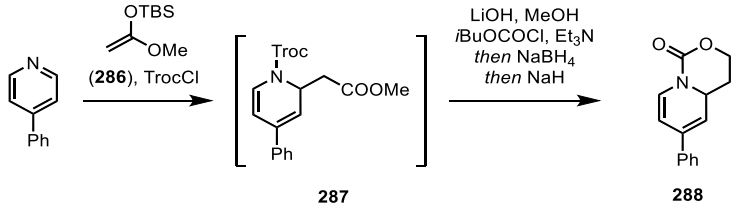


The title compound (colorless oil) was formed as the major product when dearomatization of pyridine with trimethylsilyl dimethylketene acetal in the presence of methyl chloroformate was attempted.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 6.98 – 6.74 (m, 2H), 4.85 – 4.68 (m, 2H), 3.80 (s, 3H), 3.68 (s, 3H), 3.35 (m, 1H), 1.13 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 177.5, 152.0, 124.9, 124.6, 106.3, 106.0, 53.6, 52.0, 47.4, 40.6, 21.7, 21.5.

Synthesis of 6-phenyl-4,4a-dihydro-1H,3H-pyrido[1,2-c][1,3]oxazin-1-one (**288**)



A flame dried 100 mL two neck round bottom flask was charged with 4-phenylpyridine (465 mg, 3.0 mmol, 1.0 eq.) and anhydrous DCM (30 mL, 0.1 M) under nitrogen atmosphere. The resulting solution was cooled to 0°C in an ice bath. TrocCl (420 μL, 1.539 g/mL, 5.9 mmol, 1.0 eq.) was added dropwise via syringe and the resulting mixture was stirred for 30 min at the same temperature and then cooled to -78 °C. *Tert*-butyl((1-methoxyvinyl)oxy)dimethylsilane (**286**, 1.3 mL, 0.854 g/mL, 5.0 mmol, 2.0 eq.) was then added in one portion via syringe. Without removing the cooling bath, the resulting mixture was left to warm up slowly to room temperature overnight. Solvent was removed under reduced pressure and the residue directly loaded onto a column. Isocratic elution with hexanes : EtOAc = 100 : 10 afforded the corresponding 1,2-dihydropyridine **287**.

1,2-dihydroypridine **287** was dissolved in a mixture of THF (25 mL) and MeOH (12.5 mL) under nitrogen atmosphere. LiOH (750 mg, 31.3 mmol) was added in one portion and the resulting solution was heated to 50 °C. After 1 h TLC analysis revealed full consumption of starting material. After cooling to room temperature, the reaction mixture was partitioned between EtOAc and 1 M HCl. The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the corresponding acid.

The crude acid was dissolved in THF (11 mL) and the resulting solution was cooled to 0 °C. *Iso*-butyl chloroformate (540 μL, 1.040 g/mL, 4.1 mmol) and triethylamine (590 μL, 0.726 g/mL, 4.2 mmol) were added. The reaction mixture was brought to room temperature and then filtered to remove ammonium salts. The filtrate was concentrated under reduced pressure, cooled to 0 °C and redissolved in MeOH (11 mL). $NaBH_4$ (318 mg, 8.4 mmol) was added, and the resulting mixture was brought to room temperature. After completion, the reaction mixture was quenched with water and extracted with EtOAc. The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification via flash column chromatography (SiO_2, gradient elution, hexanes : EtOAc = 100 : 50 ⟶ 100 : 70) yielded the desired alcohol.

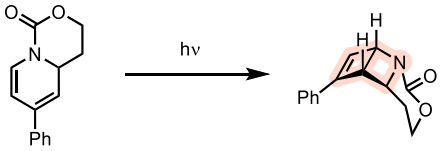
The crude alcohol was dissolved in THF (5.2 mL), and the resulting solution was cooled to 0 °C in an ice bath. NaH (66 mg, 60% w/w in mineral oil) was added to the resulting solution in one portion. The ice bath was removed, and the reaction mixture was allowed to warm up to room temperature. When TLC analysis showed complete consumption of starting material, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification via flash column chromatography (SiO_2, gradient elution, hexanes : EtOAc = 100 : 50 ⟶ 100 : 100) yielded the desired dihydropyridine (**288**, 108 mg, 0.47 mmol, 16% over 4 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 5H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.83 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.51 (s, 1H), 4.67 (ddd, *J* = 11.0, 4.8, 2.3 Hz, 1H), 4.44 – 4.28 (m, 2H), 2.42 – 2.22 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 137.9, 136.4, 128.7, 128.5, 128.2, 125.7, 116.8, 109.8, 66.0, 53.3, 27.4.

MS (ESI-Q) calculated for $C_{14}H_{13}NO_2$+H^+: 228, found: 228.

Synthesis of 4-phenyl-9-oxa-1-azatricyclo[4.4.0.0^{2,5}]dec-3-en-10-one (**289**)



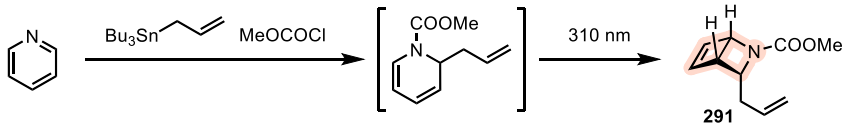
288 **289**

DCM solution (2.2 mL, 0.2 M) of the 1,2-dihydropyridine **288** (100 mg, 0.44 mmol) in a quartz test tube was degassed by sparging with argon for 2 minutes in an ultrasonic bath. Degassed solution was then irradiated in a Rayonet photoreactor equipped with 310 nm lamps for 38 h. Solvent was removed and crude product was directly loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 80 ⟶ 100 : 180 afforded 39.4 mg of recovered starting material and the desired 4-phenyl-9-oxa-1-azatricyclo[4.4.0.0^{2,5}]dec-3-en-10-one (**289**, 18.4 mg , 0.08 mmol, 18%, 30% BRSM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 5H), 6.72 (d, *J* = 2.4 Hz, 1H), 5.17 (d, *J* = 3.3 Hz, 1H), 4.45 (ddd, *J* = 11.1, 4.1, 1.9 Hz, 1H), 4.13 (td, *J* = 12.0, 11.1, 2.1 Hz, 1H), 4.04 (ddd, *J* = 11.7, 4.9, 2.8 Hz, 1H), 2.18 (ddt, *J* = 13.4, 4.5, 2.0 Hz, 1H), 1.95 (qd, *J* = 12.8, 4.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 152.7, 132.3, 129.9, 129.4, 128.8, 125.4, 67.3, 65.0, 60.8, 46.0, 27.0.

Synthesis of 3-allyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**291**)



291

Following the reported procedure[143], a flame dried 50 mL two-neck round bottom flask was charged with pyridine (180 μL, 0.978 g/mL, 2.23 mmol, 1.1 eq.), allyltributylstannane (630 μL, 1.068g/mL, 2.03 mmol, 1.0 eq.) and anhydrous DCM (4 mL, 0.6 M) under nitrogen atmosphere. Reaction mixture was cooled to 0 °C in an ice bath and methyl chloroformate (200 μL, 1.220 g/mL, 2.58 mmol, 1.3 eq.) was then added dropwise. After the addition was complete, the ice bath was removed, and the reaction

mixture was left to warm up to room temperature. Afterwards, the reaction mixture was stirred for 2 hours. Solvent was removed and the residue was directly loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 1 ⟶ 100 : 8 afforded the corresponding 1,2-dihydropyridine (288.7 mg, 1.61 mmol, 79%).

Acetone solution (16 mL, 0.2 M) of the 1,2-dihydropyridine (560.5 mg, 3.13 mmol) in a quartz test tube was degassed by sparging with argon for 3 minutes in an ultrasonic bath. Degassed solution was then irradiated in a Rayonet photoreactor equipped with 310 nm lamps for 40 hours. Solvent was removed and crude product was directly loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 40 afforded methyl 3-allyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**291**, 102.1 mg, 0.57 mmol, 18%) as a colorless clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 6.53 (bs, 1H), 6.37 (s, 1H), 5.79 – 5.66 (m, 1H), 5.12 – 5.00 (m, 2H), 4.75 (m, 1H), 4.16 (s, 1H), 3.66 (s, 3H), 3.54 (s, 1H), 2.71 (m, 1H), 2.37 – 2.21 (m, 1H).

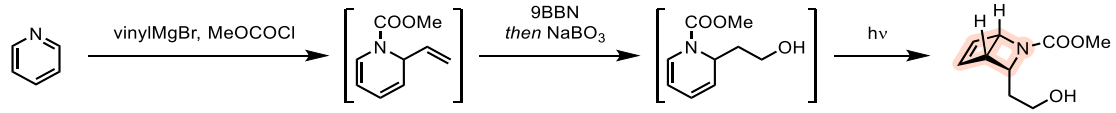
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 157.0, 156.1, 142.4, 140.6, 133.4, 117.2, 63.4, 62.5, 59.6, 59.0, 52.1, 42.6, 42.3, 35.2, 34.5.

R_f = 0.45 (hexanes : EtOAc = 4 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2992 (w), 2953 (w), 1704 (s), 1558 (w), 1450 m), 1382 (m), 1193 (w), 1159 (w), 1126 (w), 768 (w).

HRMS (ESI-TOF) calculated for $C_{10}H_{13}NO_2+H^+$: 180.1025, found 180.1026.

Synthesis of methyl 3-(2-hydroxyethyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**294**)



292 **293** **294**

A 100 mL flame dried two necked round bottom flask was charged with pyridine (2.5 mL, 31 mmol, 0.982 g/mL, 1.6 eq.) and anhydrous THF (30 mL, 0.1 M). The resulting solution was cooled to 0 °C and vinyl magnesium bromide (20 mL, 1.0 M, 20 mmol, 1.0 eq.) was added in one portion. Methyl chloroformate (1.6 mL, 21 mmol. 1.220 g/mL, 1.0 eq.) was added dropwise and the resulting mixture was left stirring at 0 °C for 30 min. Afterwards, it was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (100 mL). The organic phase was separated from the aqueous phase, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Crude product was purified by filtration through a plug of silica with hexanes : EtOAc = 100 : 10 to yield methyl 2-vinylpyridine-1(2H)-carboxylate (**292**, 2.36 g, 14.3 mmol, 71%) as a colorless clear oil.

A 100 mL flame dried two necked round bottom flask was charged with methyl 2-vinylpyridine-1(2H)-carboxylate (**292**, 2.36 g, 14.3 mmol, 1 eq). The flask was evacuated and filled with nitrogen three times. The flask was cooled to 0 °C. 9BBN (29 mL, 0.5 M solution in THF, 14.5 mmol, 1.0 eq.) was added and the resulting solution was left to warm to room temperature and stirred overnight under nitrogen atmosphere. The reaction mixture was again cooled to 0 °C and 30 mL of water followed by sodium perborate tetrahydrate (6.787 g, 42.9 mmol, 3.0 eq.) were added sequentially. The ice bath was removed, and the resulting suspension was allowed to warm to room temperature with vigorous stirring. A small exotherm was observed and the temperature was controlled with the ice bath. After stirring for 2 hours at room temperature, the reaction mixture was filtered through cotton wool and

partitioned between EtOAc and brine (50 mL each). The organic phase was separated from the aqueous phase. The latter was extracted with another portion of EtOAc (50 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 100 ⟶ 100 : 200 afforded the corresponding alcohol (**293**, 1.928 g, 10.5 mmol, 73%) as a colorless oil.

Acetone solution (53 mL, 0.2 M) of the alcohol **293** (1.928 g, 10.5 mmol) was degassed by sparging with argon for 3 minutes in an ultrasonic bath. The degassed solution was then irradiated in a Rayonet photoreactor equipped with 310 nm lamps for 1 week. Solvent was removed and crude product was directly loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 100 ⟶ 100 : 200 afforded methyl 3-(2-hydroxyethyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**294**, 0.506 g, 2.76 mmol, 26%) as a colorless clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.52 (s, 1H), 6.41 (t, *J* = 2.9 Hz, 1H), 4.82 (t, *J* = 3.3 Hz, 1H), 4.33 – 4.27 (m, 1H), 3.68 (m, 5H), 3.60 (m, 1H), 1.99 – 1.79 (m, 2H).

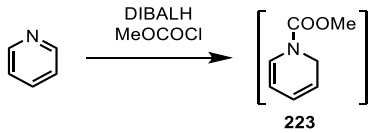
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 142.4, 141.5, 64.5, 60.1, 58.7, 52.54, 43.1, 35.5.

R_f = 0.35 (hexanes : EtOAc = 1 : 2; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3431 (bs), 2954 (w), 2878 (w), 1681 (s), 1456 (s), 1388 (m), 1194 (w), 1160 (w), 1138 (w), 1110 (w), 1055 (w).

HRMS (ESI-TOF) calculated for $C_9H_{13}NO_3$+Na^+: 206.0788, found: 206.0786.

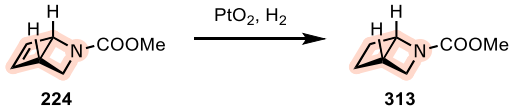
Dearomatization of pyridine under homogenous conditions



223

Following the reported procedure[90], a 50 mL flame fried round bottom flask was charged with pyridine (200 μL, 0.982 g/mL, 2.5 mmol, 1.0 eq.) and DCM (5.0 mL). The resulting solution was cooled to -78 °C in an acetone/dry ice bath. MeOCOCl (220 μL, 1.220 g/mL, 2.8 mmol, 1.1 eq.) was slowly added and the resulting mixture was left stirring for 30 minutes at the same temperature. DIBALH (1M in DCM, 5.2 mL, 5.2 mmol, 2.1 eq.) was slowly added. Dry ice was removed, and the reaction mixture was allowed to slowly warm up to room temperature. The reaction mixture was quenched with water and saturated Rochelle's salt solution was added. The resulting mixture was vigorously stirred until most of the solid dissolved. Layers were separated and the aqueous phase extracted two more times with DCM (3 x 20 mL in total). Combined organic phases were dried over $MgSO_4$, passed through a neutral alumina plug and concentrated under reduced pressure to yield 1,2-dihydropyiridne (**223**, 203 mg, 1.5 mmol, 59% yield) as a clear colorless oil.

Synthesis of methyl 2-azabicyclo[2.2.0]hexane-2-carboxylate (**313**)



224 **313**

A 4 mL vial was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 50.0 mg, 0.359 mmol, 1.0 eq.), MeOH (2.6 mL, 0.14 M) and PtO_2 hydrate (8.2 mg, 0.065 mmol, 9 mol%). The resulting suspension was purged with hydrogen for 1 minute and left stirring for 1 hour under hydrogen atmosphere (balloon). The suspension was filtered through a pad of celite to yield methyl 2-azabicyclo[2.2.0]hexane-2-carboxylate (**313**, 39.7 mg, 0.281 mmol, 78%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 4.58 (m, 1H), 4.35 – 4.25 (m, 1H), 4.00 (d, *J* = 8.1 Hz, 1H), 3.67 (s, 3H), 2.88 (m, 1H), 2.59 – 2.40 (m, 2H), 2.32 (m, 1H), 2.20 (m, 1H).

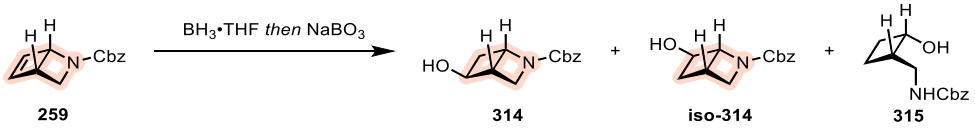
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.6, 156.2, 64.2, 63.8, 58.5, 57.6, 52.1, 31.5, 29.2, 28.9, 26.3.

R_f = 0.36 (hexanes : EtOAc = 3 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2953 (m), 1704 (s), 1449 (m), 1382 (s), 1197 (m), 1127 (m), 769 (w), 731 (w).

HRMS (ESI-TOF) calculated for $C7H_{11}NO_2$+H^+: 142.0868, found: 142.0867.

Oxidative hydroboration of benzyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**259**) with borane



259 **314** **iso-314** **315**

A flame dried 50 mL two-neck round bottom flask was charged with benzyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**259**, 750 mg, 3.5 mmol, 1.0 eq.) and anhydrous THF (14 mL) under nitrogen atmosphere. The resulting solution was cooled to -78 °C in an acetone/dry ice bath). BH_3·THF complex (1M, 3.8 mL, 3.8 mmol, 1.1 eq.) was slowly added. The reaction mixture was left to warm up to 0 °C when TLC analysis showed complete consumption of starting material. Water (14 mL) and $NaBO_3$·$4H_2O$ were added sequentially in one portion. With vigorous stirring, the resulting suspension was brought to room temperature and left stirring for 2 h. Afterwards, it was filtered through cotton wool and partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was separated and extracted with EtOAc two more times. Combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 80 ⟶ 100 : 200 afforded benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**314**, 295 mg, 1.3 mmol, 36%), benzyl 6-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-314**, 321 mg, 1.4 mmol, 39%) and benzyl ((2-hydroxycyclobutyl)methyl)carbamate (**315**, 149 mg, 0.6 mmol, 18%) as a clear colorless oils.

Benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**314**)

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.38 – 7.29 (m, 5H), 5.10 (bs, 2H), 4.65 – 4.56 (m, 1H), 4.26 m, 1H), 3.94 (m, 1H), 2.95 – 2.71 (m, 1H), 2.33 (m, 1H), 2.11 (bs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 136.8, 128.6, 128.2, 128.1, 73.4, 66.7, 59.4, 58.9, 54.3, 53.3, 41.6, 41.3, 41.1.

R_f = 0.50 (hexanes : EtOAc = 1 : 2; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3400 (bs), 2955 (w), 2883 (w), 1686 (s), 1421 (s), 1357 (m), 1100 (m), 698 (w).

HRMS (ESI-TOF) calculated for $C_{16}H_{21}NO_2$+Na^+: 256.0944, found: 256.0942.

Benzyl 6-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-314**)

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.34 (m, 5H), 5.10 (m, 2H), 4.51 – 4.37 (m, 2H), 4.26 (m, 1H), 3.90 (m, 1H), 2.87 (m, 1H), 2.63 – 2.48 (m, 1H), 2.40 – 2.14 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 155.7, 155.6, 136.8, 136.6, 73.3, 72.6, 70.5, 70.0, 66.8, 66.7, 57.2, 56.3, 37.1, 36.3, 27.4, 27.1.

R_f = 0.51 (hexanes : EtOAc = 1 : 3; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3400 (bs), 2955 (w), 2881 (w), 1686 (s), 1421 (s), 1356 (m), 1091 (m), 698 (w).

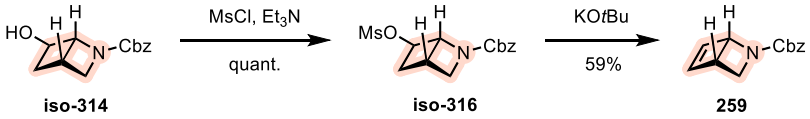
HRMS (ESI-TOF) calculated for $C_{16}H_{21}NO_2$+Na^+: 256.0944, found: 256.0941.

Benzyl ((2-hydroxycyclobutyl)methyl)carbamate (**315**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 5H), 5.28 (bs, 1H), 5.09 (s, 1H), 4.36 (q, *J* = 6.3 Hz, 1H), 3.59 – 3.48 (m, 1H), 3.25 (m, 1H), 2.52 (bs, 1H), 2.24 (dq, *J* = 12.4, 6.0 Hz, 1H), 1.91 (tt, *J* = 12.1, 6.9 Hz, 1H), 1.81 – 1.67 (m, 1H), 1.58 (tt, *J* = 10.4, 5.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 136.5, 128.7, 128.3, 128.3, 67.9, 67,0, 41.9, 40.5, 29.7, 18.2.

Mesylation and elimination



iso-314 **iso-316** **259**

A 4 mL vial was charged with benzyl 6-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-314**, 42.3 mg, 0.181 mmol, 1.0 eq.) and DCM (2.0 mL, 0.09M). The resulting solution was cooled to 0 °C in an ice bath and Et_3N (53 μL, 0.726 g/mol, 0.38 mmol, 2.1 eq) and MsCl (28 μL, 1.470 g/mL, 0.36 mmol, 2.0 eq.) were added via syringe in one portion. The ice bath was removed, and the reaction mixture was left to warm to room temperature. After TLC analysis indicated full consumption of starting material, the reaction mixture was partitioned between DCM (20 mL) and saturated $NaHCO_3$ (20 mL). The organic phase was separated, and the aqueous phase was extracted two more times with DCM (20 mL each). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 50 ⟶ 10 : 75 afforded benzyl 6-((methylsulfonyl)oxy)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-316**, 56.4 mg, 0.181 mmol, 100%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.21 – 4.92 (m, 3H), 4.66 (bs, 1H), 4.38 – 4.22 (m, 1H), 3.97 (d, *J* = 8.7 Hz, 1H), 3.12 (m, 1H), 3.00 (m, 1H), 2.82 – 2.62 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 155.3, 154.9, 136.3, 136.0, 128.7, 128.6, 128.5, 128.39, 128.2, 79.4, 79.0, 68.3, 67.8, 67.5, 67.1, 57.1, 56.2, 38.0, 37.8, 35.7, 35.5, 28.1, 27.8.

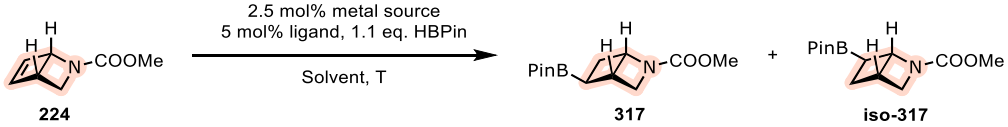
R_f = 0.69 (hexanes : EtOAc = 1 : 2; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3028 (w), 2956 (w), 2887 (w), 1707(s), 1603 (m), 1417 (m), 1357 (m), 1178 (m), 1123 (w), 970 (m), 900 (w), 823 (w).

HRMS (ESI-TOF) calculated for $C_{14}H_{17}NO_5S+Na^+$: 334.0720, found: 334.0719.

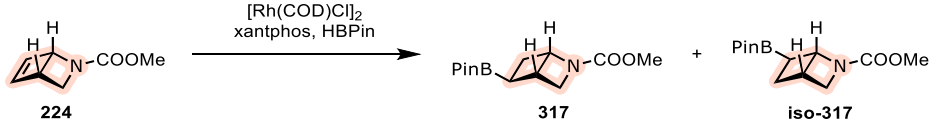
In an argon filled glovebox, a 4 mL vial was charged with benzyl 6-((methylsulfonyl)oxy)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-316**, 44.5 mg, 0.143 mmol, 1.0 eq.) and KO*t*Bu (18.2 mg, 0.162 mmol, 1.1 eq.). The vial was taken outside of the glovebox and anhydrous *tert*-BuOH (1.0 mL, 0.1 M) was added. The resulting solution was stirred for 3 h at 70 °C under argon atmosphere. Afterwards, the reaction mixture was partitioned between Et_2O (50 mL) and water (50 mL). The organic phase was separated, washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 10 : 30 afforded benzyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**259**, 18.2 mg, 0.085 mmol, 59%) as a colorless oil, the spectroscopic data of which matched reported values from the literature.[74]

General procedure for the transition metal catalyzed hydroboration screening



A 4 mL vial was charged with rhodium source (2.5 mol%) and ligand (5 mol%; 10 mol% for monodentate ligands) in an argon filled glovebox. The vial was taken outside the glovebox and anhydrous solvent (0.5 M total concentration) was added. The resulting mixture was stirred for 1 minute. Substrate stock solution (**224**, 1.0 M) and HBpin (1.1 eq.) were added sequentially via syringe. The resulting mixture was stirred for 3 hours under argon atmosphere. The solvent was removed, and the residue was loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 15 ⟶ 100 : 20 afforded a mixture of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**317**) and methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-317**) as a colorless film. Isomer ratio was determined with ^{1}H NMR analysis.

Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**317**) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-317**)



A flame dried 4 mL vial was charged with $[Rh(COD)Cl]_2$ (12.7 mg, 0.026 mmol, 1.4 mol%) and xantphos (29.5 mg, 0.051 mmol, 2.8 mol%) in a nitrogen filled glovebox. The vial was taken outside the glovebox and THF (0.5 mL) was added. The resulting mixture was stirred for 5 minutes at room temperature. Afterwards, THF (0.5 mL) solution of methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 0.250 g, 1.80 mmol, 1.0 eq.) and HBPin (350 μL, 0.882 g/mL, 2.41 mmol, 1.3 eq.) were added in one portion via syringe. The resulting reaction mixture was stirred at room temperature overnight, the solvent was removed, and the residue loaded onto a column. Isocratic elution with hexanes : EtOAc = 100 : 50 afforded a 1.7 : 1 mixture of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-

azabicyclo[2.2.0]hexane-2-carboxylate (**317**) and methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-317**, 0.439 g, 1.64 mmol, 92% combined yield) as a colorless clear oil. For characterization purposes, the constitutional isomers were separated using Sepiatec preparative chiral SFC (IG 21x250mm column, 70 mL/min flow rate, 10% MeOH & 0.1% NH_4OH modifiers, 215 nm UV detection).

6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-317**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 4.54 (m, 1H), 4.29 – 4.24 (m, 1H), 4.01 – 3.97 (m, 1H), 3.64 (s, 4H), 2.88 (m, 1H), 2.40 – 2.27 (m, 3H), 1.23 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 138.0, 137.3, 83.5, 64.6, 57.6, 52.1, 31.3, 28.0, 25.9, 24.8.

^{11}B NMR (160 MHz, $CDCl_3$) δ 32.9.

R_f = 0.55 (hexanes : EtOAc = 3 : 2; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2977 (w), 2878 (w), 1705 (s), 1449 (m), 1373 (s), 1320 (w), 1142 (s), 983 (w), 769 (w).

HRMS (ESI-TOF) calculated for $C_{13}H_{22}NO_4B+H^+$: 268.1720, found: 248.1719.

5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**317**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 4.52 (m, 1H), 4.27 – 4.20 (m, 1H), 3.94 (m, 1H), 3.60 (s, 3H), 2.81 – 2.76 (m, 1H), 2.48 – 2.27 (m, 2H), 2.10 – 2.03 (m, 1H), 1.19 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.5, 156.2, 83.5, 63.9, 63.4, 59.7, 58.7, 52.0, 32.6, 30.6, 30.3, 24.7, 22.7.

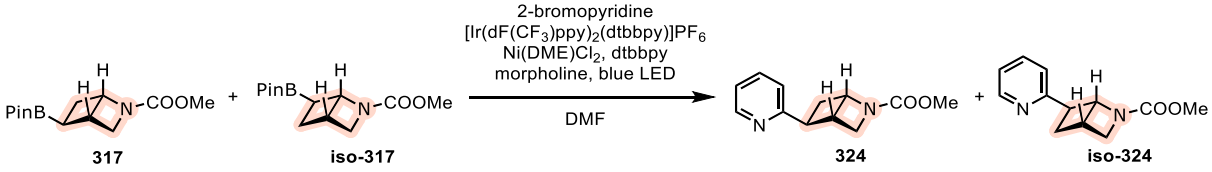
^{11}B NMR (160 MHz, $CDCl_3$) δ 33.5.

R_f = 0.55 (hexanes : EtOAc = 3 : 2; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2977 (w), 2878 (w), 1705 (s), 1449 (m), 1373 (s), 1320 (w), 1142 (s), 983 (w), 769 (w).

HRMS (ESI-TOF) calculated for $C_{13}H_{22}NO_4B+H^+$: 268.1720, found: 248.1719.

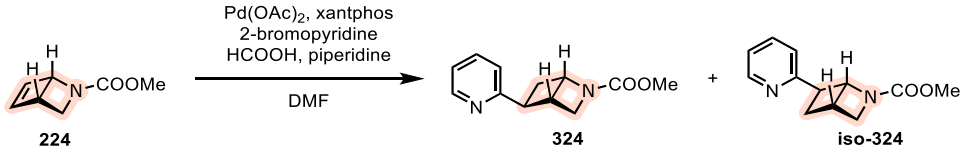
Synthesis of methyl 5-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**324**) and methyl 6-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-324**) via dual photo/nickel catalyzed cross-coupling



Following the reported procedure[105], a 4 mL vial was charged with Ni(DME)Cl_2 (5.5 mg, 0.025 mmol,) and dtbbpy (6.7 mg, 0.025 mmol) in a nitrogen filed glovebox. The vial was taken outside the glovebox and DMF (2.5 mL) was added. The resulting suspension was sonicated for 30 seconds and afterwards heated with a heat gun until a clear green solution was obtained. A second 4 mL vial was charged with

($Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (2.0 mg, 0.002 mmol, 3 mol%), 2-bromopyridine (5 μL, 1.66 g/mL, 0.05 mmol, 1.0 eq.), a 1.7 : 1 mixture of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**317**) and methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-317**) (26.7 mg, 0.10 mmol, 2.0 eq.), morpholine (8 μL, 1.030 g/mL, 0.2 mmol, 2.0 eq.) and DMF (0.25 mL). 0.25 mL of [Ni] stock solution was added and the resulting mixture was irradiated using blue LEDs for 3 hours. Solvent was removed under high vacuum and the residue loaded onto a column. Gradient elution with hexanes : EtOAc = 1 : 1 ⟶ pure EtOAc afforded a mixture of methyl 5-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate and methyl 6-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**324**) methyl 6-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-324**) (4.2 mg, 0.019 mmol, 40% combined yield) as a colorless film. Spectroscopic data matched the products of the reductive Heck reaction with 2-bromopyridine. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

Synthesis of methyl 5-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**324**) and methyl 6-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-324**) via reductive Heck



A 4 mL vial was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 70 mg, 0.50 mmol, 1.0 eq.), DMF (2.5 mL, 0.2 M), 2-bromopyridine (100 μL, 1.657 g/mL 1.05 mmol, 2.0 eq.), piperidine (150 μL, 0.862 g/mL, 1.52 mmol, 3.0 eq.), formic acid (40 μL, 1.220 g/mL, 1.1 mmol, 2.1 eq.), $Pd(OAc)_2$ (6.0 mg, 0.027 mmol, 5 mol%) and xantphos (29.0 mg, 0.050 mmol 10 mol%). The resulting mixture was sealed with a septum and degassed by sparging with argon for 5 minutes. After stirring at 70 °C for 8 hours, the volatiles were removed under high vacuum and the residue loaded onto a column. Isocratic elution with EtOAc followed by further purification with reverse phase liquid chromatography afforded a mixture of methyl 5-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate and (**324**) methyl 6-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (iso-**324**) as a colorless clear oil (68 mg, 0.31 mmol, 62% combined yield). *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.* For characterization purposes, the constitutional isomers were separated using Sepiatec preparative SFC (IB-N 21x250mm column, 70 mL/min flow rate, 20% *i*PrOH & 0.1% NH_4OH modifiers, 215 nm UV detection).

Methyl 6-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-324**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 8.54 (m, 1H), 7.57 (m, 1H), 7.15 – 7.04 (m, 2H), 4.73 – 4.57 (m, 1H), 4.34 (m, 1H), 4.25 – 4.06 (m, 1H), 3.83 (m, 1H), 3.66 (s, 3H), 3.17 – 2.94 (m, 1H), 2.94 – 2.49 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 163.3, 161.9, 161.7, 156.6, 156.3, 149.5, 149.4, 136.5, 122.6, 122.1, 121.8, 121.5, 68.3, 68.0, 61.6, 61.0, 57.9, 57.0, 56.9, 52.3, 52.1, 48.9, 48.2, 46.8, 37.5, 36.3, 36.0, 31.9, 31.7, 29.0.

R_f = 0.31 (EtOAc; UV)

IR (ATR-FTIR, cm^{-1}): 2953 (w), 2879 (w), 1702 (s), 1589 (8), 1450 (s), 1382 (s), 1195 (m), 1152 (m), 1129 (m), 770 (w).

HRMS (ESI-TOF) calculated for $C_{12}H_{14}N_2O_2+H^+$: 219.1134, found: 219.1134.

Methyl 5-(pyridin-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**324**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 8.64 – 8.51 (m, 1H), 7.64 – 7.50 (m, 1H), 7.16 (m, 2H), 4.62 (m, 1H), 4.36 (m, 1H), 4.12 (m, 1H), 3.88 (m, 1H), 3.68 (s, 3H), 3.01 (m, 1H), 2.91 (dm, 1H), 2.59 (m, 1H).

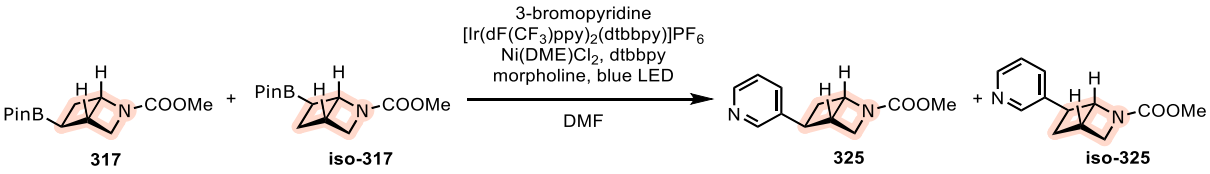
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 162.0, 161.8, 156.4, 156.1, 149.6, 149.5, 136.6, 122.7, 122.2, 121.6, 68.4, 68.0, 58.0, 57.0, 52.3, 52.2, 49.0, 48.3, 32.0, 31.8, 29.1.

R_f = 0.31 (EtOAc; UV)

IR (ATR-FTIR, cm^{-1}): 2953 (w), 2879 (w), 1702 (s), 1589 (8), 1450 (s), 1382 (s), 1195 (m), 1152 (m), 1129 (m), 770 (w).

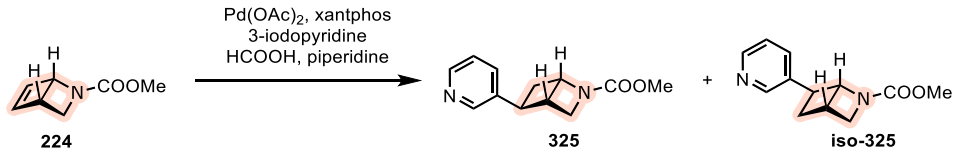
HRMS (ESI-TOF) calculated for $C_{12}H_{14}N_2O_2+H^+$: 219.1134, found: 219.1134.

Synthesis of methyl 5-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**325**) and methyl 6-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-325**) via dual photo/nickel catalyzed cross-coupling



Following the reported procedure[105], a 4 mL vial was charged with $Ni(DME)Cl_2$ (1.1 mg, 0.005 mmol, 5 mol%) and dtbbpy (2.0 mg, 0.007 mmol, 7 mol%) in a nitrogen filed glovebox. The vial was taken outside the glovebox and DMF (0.5 mL) was added. The resulting suspension was sonicated for 30 seconds and afterwards heated with a heat gun until a clear green solution was obtained. A second 4 mL vial was charged with $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (1.1 mg, 0.001 mmol, 1 mol%), 3-bromopyridine (10 μL, 1.64 g/mL, 0.10 mmol, 1.0 eq.), a 1.7 : 1 mixture of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**317**) and methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso**-**317**) (53.4 mg, 0.20 mmol, 2.0 eq.), morpholine (13 μL, 1.030 g/mL, 0.15 mmol, 1.5 eq.) and DMF (0.5 mL). Both solutions were thoroughly mixed and irradiated using blue LEDs for 2 hours. Solvent was removed under high vacuum and the residue loaded onto a column. Isocratic elution with EtOAc + 1% Et_3N afforded a 1.8 : 1 mixture of methyl 5-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**325**) and methyl 6-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-325**) (15.9 mg, 0.073 mmol, 70% combined yield) as a colorless oil. Spectroscopic data matched the products of the reductive Heck reaction with 3-iodopyridine.

Synthesis of methyl 5-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**325**) and methyl 6-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-325**) via reductive Heck



224 325 iso-325

A 20 mL round bottom flask was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 97.3 mg, 0.699 mmol, 1.0 eq.), DMF (3.5 mL, 0.2 M), 3-iodopyridine (287 mg, 1.40 mmol, 2.0 eq.), piperidine (210 μL, 0.862 g/mL, 2.13 mmol, 3.0 eq.), formic acid (56 μL, 1.220 g/mL, 2.92 mmol, 2.0 eq.), $Pd(OAc)_2$ (8.4 mg, 5 mol%) and xantphos (40.6 mg, 10 mol%). The resulting mixture was sealed with a septum and degassed by sparging with argon for 5 minutes. After stirring at 30 °C overnight, the reaction mixture was partitioned between EtOAc and brine (20 mL each). The organic phase was separated, and the aqueous phase extracted two more times with EtOAc (20 mL). Combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure Crude NMR analysis indicated the formation of a 1 : 1 mixture of constitutional isomers. The residue after solvent evaporation was loaded onto a column. Isocratic elution with EtOAc + 1% Et_3N yielded a mixture of methyl 6-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-325**) and methyl 5-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**325**) as a colorless clear oil (149.5 mg, 0.685 mmol, 98% combined yield). For characterization purposes, the constitutional isomers were separated using Sepiatec preparative SFC (IZ 21x250mm column, 70 mL/min flow rate, 20% *i*PrOH & 0.1% NH_4OH modifiers, 215 nm UV detection).

Methyl 6-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-325**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 8.48 (m, 2H), 7.57 (m, 1H), 7.26 (s, 1H), 4.50 (m, 1H), 4.37 (t, *J* = 7.7 Hz, 1H), 4.13 (d, *J* = 7.5 Hz, 1H), 3.82 (m, 1H), 3.69 (s, 3H), 2.99 (ns, 1H), 2.72 (m, 1H), 2.59 (bs, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.3, 156.1, 148.4, 148.1, 147.8, 147.7, 138.5, 134.55, 134.0, 123.7, 69.2, 68.7, 58.0, 57.0, 52.4, 52.3, 45.1, 44.5, 33.0, 32.8, 28.8.

R_f = 0.27 (EtOAc + 1% Et_3N; UV)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2880 (w), 1702 (s), 1450 (s), 1383 (s), 1198 (m), 1131 (m), 715 (w).

HRMS (ESI-TOF) calculated for $C_{12}H_{14}N_2O_2$+H^+: 219.1134, found: 219.1138.

Methyl 5-(pyridin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**325**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 8.47 (m, 2H), 7.55 (d, *J* = 6.5 Hz, 1H), 7.26 (m, 1H), 4.70 (m, 1H), 4.39 (t, *J* = 7.6 Hz, 1H), 4.14 (d, *J* = 8.8 Hz, 1H), 3.79 (m, 1H), 3.69 (s, 3H), 2.94 (dm, 2H), 2.55 (m, 1H).

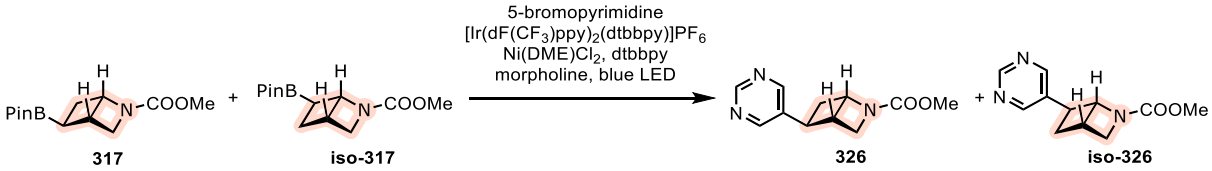
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.6, 156.4, 148.1, 147.7, 140.3, 134.2, 123.7, 61.3, 60.8, 58.0, 57.1, 52.3, 42.7, 38.4, 37.9, 37.6.

R_f = 0.27 (EtOAc + 1% Et_3N; UV)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2880 (w), 1702 (s), 1450 (s), 1383 (s), 1198 (m), 1131 (m), 715 (w).

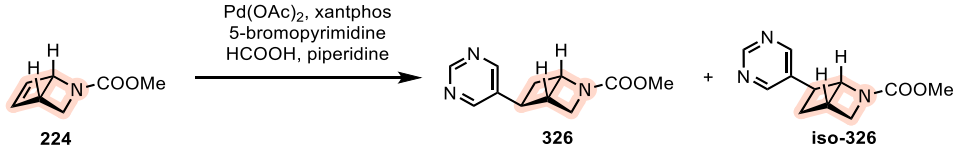
HRMS (ESI-TOF) calculated for $C_{12}H_{14}N_2O_2$+H^+: 219.1134, found: 219.1138.

Synthesis of methyl (5-(pyrimidin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**326**) and methyl (6-(pyrimidin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-326**) via dual photo/nickel catalyzed cross-coupling



Following the reported procedure[105], a 4 mL vial was charged with $Ni(DME)Cl_2$ (2.2 mg, 0.010 mmol, 5 mol%) and dtbbpy (2.7 mg, 0.010 mmol, 5 mol%) in a nitrogen filed glovebox. The vial was taken outside the glovebox and DMF (1 mL) was added. The resulting suspension was sonicated for 30 seconds and afterwards heated with a heat gun until a clear green solution was obtained. A second 4 mL vial was charged with $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (2.3 mg, 0.002 mmol, 1 mol%), 5-bromopyrimidine (31.8 mg, 0.20 mmol, 1.0 eq.), a 1.7 : 1 mixture of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**317**) and methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-317**) (106.8 mg, 0.40 mmol, 2.0 eq.), morpholine (26 μL, 1.030 g/mL, 0.30 mmol, 1.5 eq.) and DMF (1 mL). Both solutions were thoroughly mixed and irradiated using blue LEDs for 2 hours. Solvent was removed under high vacuum and the residue loaded onto a column. Isocratic elution with hexanes : acetone = 1 : 1 + 1% Et_3N afforded a 1.1 : 1 mixture of methyl (5-(pyrimidin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**326**) and methyl (6-(pyrimidin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-326**) (36.4 mg, 0.166 mmol, 83% combined yield) as a colorless oil. Spectroscopic data matched the products of the reductive Heck reaction with 5-bromopyrimidine.

Synthesis of methyl (5-(pyrimidin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**326**) and methyl (6-(pyrimidin-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-326**) via reductive Heck



A 4 mL vial was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 70 mg, 0.50 mmol, 1.0 eq.), DMF (2.5 mL, 0.2 M), 5-bromopyrimidine (159 mg, 1.00 mmol, 2.0 eq.), piperidine (150 μL, 0.862 g/mL, 1.52 mmol, 3.0 eq.), formic acid (40 μL, 1.220 g/mL, 1.1 mmol, 2.1 eq.), $Pd(OAc)_2$ (6.0 mg, 0.027 mmol, 5 mol%) and xantphos (29.0 mg, 0.050 mmol 10 mol%). The resulting mixture was sealed with a septum and degassed by sparging with argon for 5 minutes. After heating at 70 °C for 2 hours, the volatiles were removed under high vacuum and the residue loaded onto a column. Isocratic elution with EtOAc + 1% Et_3N afforded a 1 : 1 mixture of methyl 6-(pyrimidin-5-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate and (**iso-326**) methyl 5-(pyrimidin-5-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**326**) as a colorless clear oil (113 mg, 0.51 mmol, quant. combined yield). For characterization purposes, the constitutional isomers were separated using Sepiatec preparative SFC (IB-N 21x250mm column, 70 mL/min flow rate, 20% MeOH & 0.1% NH_4OH modifiers, 215 nm UV detection).

Methyl 6-(pyrimidin-5-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-326**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 9.11 (s, 1H), 8.66 (m, 2H), 4.54 (m, 1H), 4.41 (t, *J* = 7.8 Hz, 1H), 4.25 – 4.11 (m, 1H), 3.83 (m, 1H), 3.11 – 3.04 (m, 1H), 2.82 – 2.74 (m, 1H), 2.63 (m, 1H).

^{13}C NMR (126 MHz, CDCl3, rotamers) δ 157.2, 156.1, 155.4, 136.0, 68.7, 68.2, 68.2, 58.1, 57.1, 52.6, 52.5, 43.0, 42.3, 32.9, 32.4, 29.0.

R_f = 0.46 (DCM : MeOH = 1 : 1; UV)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2881 (w), 1697 (s), 1557 (m), 1448 (s), 1412 (w), 1380 (s), 1195 (w), 1129 (m), 769 (w).

HRMS (ESI-TOF) calculated for $C_{11}H_{13}N_3O_2+H^+$: 220.1086, found: 220.1087.

Methyl 5-(pyrimidin-5-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**326**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 9.09 (s, 1H), 8.63 (s, 2H), 4.74 (d, *J* = 13.4 Hz, 1H), 4.42 (dd, *J* = 8.9, 6.6 Hz, 1H), 4.24 – 4.11 (m, 1H), 3.80 (td, *J* = 8.1, 3.2 Hz, 1H), 3.71 (s, 3H), 3.14 – 2.89 (m, 2H), 2.68 – 2.54 (m, 1H).

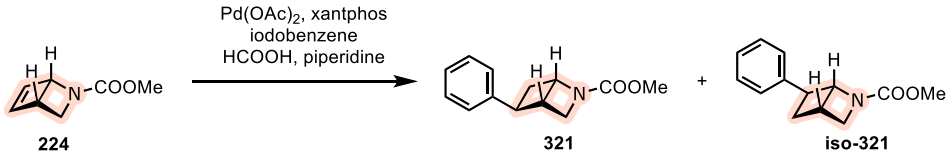
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 157.3, 156.4, 155.3, 137.8, 61.2, 60.8, 58.0, 57.0, 52.4, 40.6, 40.5, 38.2, 37.8, 37.5.

R_f = 0.46 (DCM : MeOH = 1 : 1; UV)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2881 (w), 1697 (s), 1557 (m), 1448 (s), 1412 (w), 1380 (s), 1195 (w), 1129 (m), 769 (w).

HRMS (ESI-TOF) calculated for $C_{11}H_{13}N_3O_2+H^+$: 220.1086, found: 220.1087.

Synthesis of methyl (5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**321**) and methyl (6-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-321**) via reductive Heck



A 50 mL round bottom flask was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 0.200 g, 1.437 mmol, 1.0 eq.), DMF (14 mL, 0.1 M), iodobenzene (400 μL, 3.59 mmol, 2.5 eq., 1.830 g/mL), piperidine (430 μL, 4.35 mmol, 3.0 eq., 0.862 g/mL), formic acid (110 μL, 2.92 mmol, 2.0 eq., 1.220 g/mL), $Pd(OAc)_2$ (16.1 mg, 5 mol%) and xantphos (83.2 mg, 10 mol%). The resulting mixture was sealed with a septum and degassed by sparging with argon for 5 minutes. After heating at 70 °C overnight, the reaction mixture was partitioned between Et_2O and water (50 mL each). The aqueous phase was separated, and the organic phase was washed again with water and brine. The organic phase was dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 15 afforded a 1 : 1 mixture of methyl 5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**321**) and methyl 6-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-321**) (0.297 g, 1.366 mmol, 95%) as a slightly yellow clear oil.

Methyl (5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**321**)

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.33 (m, 2H), 7.22 (m, 3H), 4.68 (broad s, 1H), 4.39 (dd, *J* = 8.7, 6.6 Hz, 1H), 4.14 (d, *J* = 8.7 Hz, 1H), 3.79 (td, *J* = 7.9, 3.1 Hz, 1H), 3.72 (s, 3H)z, 3.01 (m, 1H), 2.89 (m, 1H), 2.59 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.6, 145.1, 128.7, 126.5, 126.5, 61.4, 60.9, 58.0, 57.1, 52.3, 45.3, 38.7, 38.1, 37.8.

R_f = 0.53 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2953 (w), 2879 (w), 1706 (s), 1450 (m), 1384 (m), 1128 (w), 1129 (w).

HRMS (ESI-TOF) calculated for $C_{13}H_{15}NO_2$+Na^+: 240.0995, found: 240.0840

Methyl (6-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-321**)

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) 7.28 (m, 5H), 4.54 (broad s, 1 H), 4.38 (m, 1H), 4.14 (d, *J* = 7.6 Hz, 1H), 3.80 (m, 1 H), 3.74 (s, 3 H), 2.97 (m, 1H), 2.68 (m, 2H).

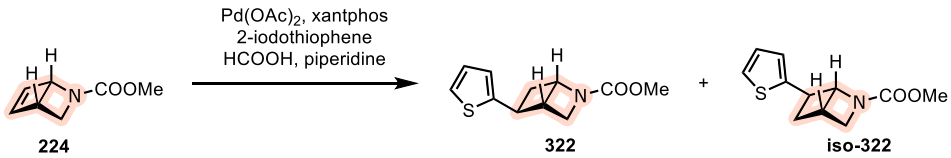
^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.5, 156.1, 143.2, 128.7, 126.6, 126.4, 69.7, 69.3, 57.9, 57.1, 52.3, 47.4, 46.9, 33.1, 28.8.

R_f = 0.59 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2953 (w), 2879 (w), 1706 (s), 1449 (m), 1383 (m), 1197 (w), 700 (w).

HRMS (ESI-TOF) calculated for $C_{13}H_{15}NO_2$+Na^+: 240.0995, found: 240.0993

Synthesis of methyl 5-(thiophen-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**322**) and methyl 6-(thiophen-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-322**) via reductive Heck



A 20 mL round bottom flask was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 97.3 mg, 0.699 mmol, 1.0 eq.), DMF (3.5 mL, 0.2 M), 2-iodothiophene (160 μL, 1.902 g/mL, 1.40 mmol, 2.0 eq.), piperidine (210 μL, 0.862 g/mL, 2.13 mmol, 3.0 eq.), formic acid (56 μL, 1.220 g/mL, 1.5 mmol, 2.0 eq.), $Pd(OAc)_2$ (8.4 mg, 5 mol%) and xantphos (40.6 mg, 10 mol%). The resulting mixture was sealed with a septum and degassed by sparging with argon for 5 minutes. After heating at 30 °C overnight, the reaction mixture was partitioned between Et_2O and brine (20 mL each). The organic phase was separated, and the aqueous phase extracted two more times with Et_2O (20 mL). Combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Crude NMR analysis indicated the formation of a 1 : 1.2 mixture of constitutional isomers. The residue after solvent evaporation was loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 15 → 100 : 30 afforded a mixture of methyl 5-(thiophen-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**322**) and methyl 6-(thiophen-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate as a colorless clear oil (**iso-322**) (154.5 mg, 0.692 mmol, 99%).

Methyl 5-(thiophen-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**322**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 7.19 – 7.15 (m, 1H), 6.96 – 6.91 (m, 1H), 6.87 – 6.80 (m, 1H), 4.67 (bs, 1H), 4.45 – 4.32 (m, 1H), 4.11 (d, *J* = 8.8 Hz, 1H), 3.99 (t, *J* = 7.6 Hz, 1H), 3.70 (s, 3H), 2.96 (m, 2H), 2.63 (dt, *J* = 13.1, 6.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.5, 149.0, 127.0, 123.6, 123.1, 61.2, 60.7, 57.7, 56.7, 52.3, 40.7, 40.4, 39.3, 39.1.

R_f = 0.27 (hexanes : EtOAc = 5 : 1; UV)

IR (ATR-FTIR, cm^{-1}): 2953 (w), 2880 (w), 1704 (s), 1449 (s), 1382 (s), 1198 (m), 1128 (m), 768 (w), 698 (w).

HRMS (ESI-TOF) calculated for $C_{11}H_{13}NO_2S+H^+$: 224.0745, found: 224.0746.

Methyl 6-(thiophen-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-322**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 7.17 (bs, 1H), 6.96 (bs, 1H), 6.88 (bs, 1H), 4.51 (bs, 1H), 4.34 (t, *J* = 7.7 Hz, 1H), 4.14 – 3.93 (m, 2H), 3.71 (s, 3H), 2.99 (bs, 1H), 2.81 – 2.72 (m, 1H), 2.69 – 2.56 (m, 1H).

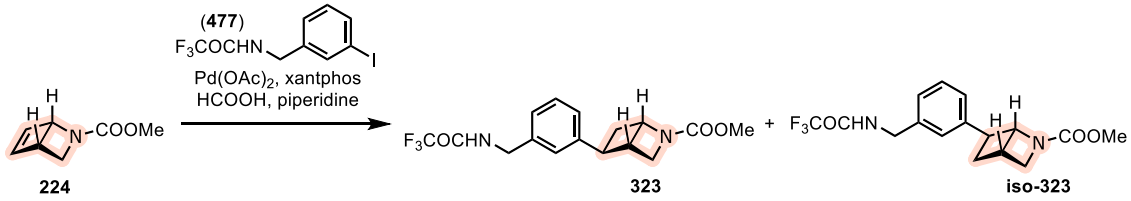
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.4, 146.9, 127.1, 123.6, 123.2, 70.3, 69.9, 57.8, 56.9, 52.3, 43.0, 42.4, 35.4, 34.9, 28.8.

R_f = 0.27 (hexanes : EtOAc = 5 : 1; UV)

IR (ATR-FTIR, cm^{-1}): 2953 (w), 2880 (w), 1704 (s), 1449 (s), 1382 (s), 1198 (m), 1128 (m), 768 (w), 698 (w).

HRMS (ESI-TOF) calculated for $C_{11}H_{13}NO_2S+H^+$: 224.0745, found: 224.0746.

Synthesis of methyl 5-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**323**) and methyl 6-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-323**)

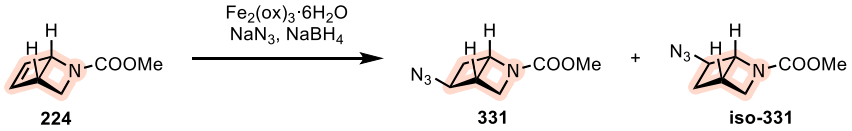


A 4 mL screw cap septum vial was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 13.9 mg, 0.10 mmol, 1.0 eq.), DMF (0.5 mL, 0.2 M), 2,2,2-trifluoro-*N*-(3-iodobenzyl)acetamide (**477**, 65.8 mg, 0.20 mmol, 2.0 eq.), piperidine (30 μL, 0.862 g/mL, 0.30 mmol, 3.0 eq.), formic acid (8 μL, 1.220 g/mL, 0.20 mmol, 2.0 eq.), $Pd(OAc)_2$ (1.2 mg, 5 mol%) and xantphos (5.8 mg, 10 mol%). The resulting mixture was degassed by sparging with argon for 3 minutes and then heated to 50 °C for 2 h in a heating block. The reaction mixture was cooled to room temperature, partitioned between Et_2O and brine (20 mL each). The organic phase was separated, and the aqueous phase extracted two more times with Et_2O (20 mL). Combined organic phases were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure, and loaded onto a column. Gradient elution with hexanes :

EtOAc = 100 : 25 → 100 : 100 afforded a mixture of methyl 5-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**323**) and methyl 6-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-323**) (29.0 mg, 0.08 mmol, 85%) as a slightly yellow clear oil. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

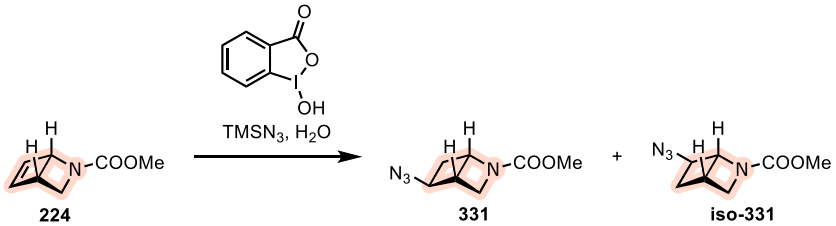
MS (ESI-Q) calculated for $C_{16}H_{17}F_3N_2O_3$+H^+: 343, found: 343.

Synthesis of methyl 5-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**331**) methyl 6-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-331**) under Boger's conditions



Following the reported procedure[95], a 20 mL round bottom flask was charged with iron(III) oxalate hexahydrate (96.0 mg, 0.2 mmol, 2.0 eq.) and water (4 mL). The resulting suspension was left stirring for 2 hours until completely homogenous. The solution was then cooled to 0 °C and degassed by sparging with argon for 10 minutes. NaN_3 (19.2 mg, 0.3 mmol, 3.0 eq.) and EtOH (2 mL) were added sequentially in one portion. Ethanol solution (2 mL, 0.05 M) of methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 13.9 mg, 0.1 mmol, 1.0 eq.) was added with a pipette. $NaBH_4$ (12.0 mg, 0.32 mmol, 3.2 eq.) was added in one portion and the resulting mixture was left stirring for 5 minutes. Another portion of $NaBH_4$ was added and the resulting mixture was left stirring for 30 minutes. The reaction mixture was quenched by adding saturated aqueous ammonia (1.0 mL) and extracted with DCM : MeOH = 10 : 1 mixture (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Isocratic elution with hexanes : EtOAc = 100 : 40 afforded a 2.0 : 1 mixture of methyl 5-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**331**) and methyl 6-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-331**) (9.4 mg, 0.05 mmol, 52% combined yield) as a colorless film.

Synthesis of methyl 5-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**331**) methyl 6-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-331**) under Xu's conditions



Following the reported procedure[94], a flame dried 4 mL vial was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 99.7 mg, 0.716 mmol, 1.0 eq.), 1-hydroxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (27.0 mg, 0.100 mmol, 14 mol%) and anhydrous DCM (0.2 mL) under nitrogen atmosphere. Water (18 μL, 1.000 g/mL, 1.0 mmol, 1.4 eq.) and $TMSN_3$ (240 μL, 0.868 g/mL, 1.8 mmol, 2.5 eq.) were added sequentially in one portion. The resulting mixture was stirred vigorously for 5 hours at room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted with DCM (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 30 ⟶ 100 : 40

afforded a 1 : 2.1 mixture of methyl 5-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**331**) and methyl 6-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-331**) (77.7 mg, 0.427 mmol, 60%) as a colorless clear oil.

Methyl 6-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-331**)

^{1}H NMR (499 MHz, $CDCl_3$, rotamers) δ 4.49 (m, 1H), 4.32 – 4.26 (m, 1H), 4.18 (m, 1H), 3.94 (m, 1H), 3.69 (s, 3H), 3.00 – 2.88 (m, 1H), 2.62 (m, 1H), 2.41 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.0, 68.1, 67.6, 61.3, 60.7, 57.6, 56.6, 52.6, 34.1, 33.6, 28.4.

R_f = 0.63 (hexanes : EtOAc = 3 : 2; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2956 (w), 2885 (w), 2096 (s), 1705 (s), 1449 (m), 1382 (m), 1246 (w), 1199 (w), 1131 (w), 769 (w).

HRMS (ESI-TOF) calculated for $C_7H_{10}N_4O_2$+H^+: 183.0882, found: 183.0886.

Methyl 5-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**331**)

^{1}H NMR (499 MHz, ^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.44 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.1 Hz, 1H), 4.71 (d, *J* = 22.6 Hz, 1H), 4.19 (dd, *J* = 9.9, 7.8 Hz, 0H), 3.83 – 3.69 (m, 1H), 3.69 – 3.56 (m, 2H), 3.34 – 3.27 (m, 1H), 3.20 – 2.90 (m, 1H).

δ 4.59 (m, 1H), 4.30 (dd, *J* = 9.2, 7.1 Hz, 1H), 4.28 – 4.17 (m, 1H), 3.98 (dd, *J* = 9.2, 1.6 Hz, 1H), 3.67 (s, 3H), 2.97 (s, 1H), 2.80 (m, 1H), 2.49 (dt, *J* = 13.3, 5.6 Hz, 1H).

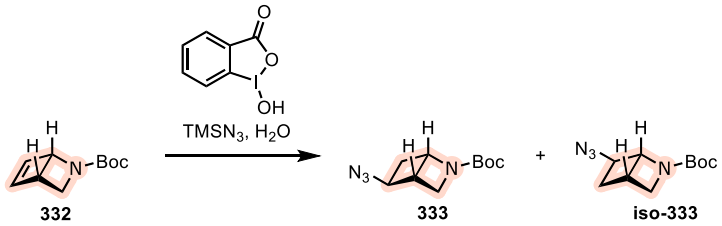
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.3, 60.7, 60.1, 59.6, 55.3, 54.4, 52.4, 38.8, 37.7, 37.4.

R_f = 0.63 (hexanes : EtOAc = 3 : 2; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2956 (w), 2885 (w), 2096 (s), 1705 (s), 1449 (m), 1382 (m), 1246 (w), 1199 (w), 1131 (w), 769 (w).

HRMS (ESI-TOF) calculated for $C_7H_{10}N_4O_2$+H^+: 183.0882, found: 183.0886.

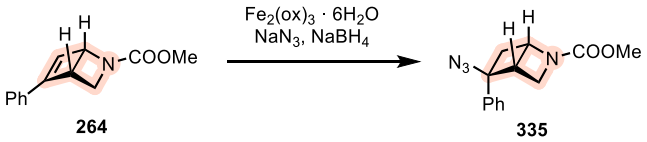
Synthesis of *tert*-butyl 5-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**333**) *tert*-butyl 6-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-333**) under Xu's conditions



Following the reported procedure[94], a flame dried 4 mL vial was charged with *tert*-butyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**332**, 34.5 mg, 0.19 mmol), 1-hydroxy-1λ^3-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (27.0 mg, 0.100 mmol, 54 mol%) and anhydrous DCM (0.2 mL) under nitrogen atmosphere. Water (18 μL, 1.000 g/mL, 1.0 mmol, 5.2 eq.) and $TMSN_3$ (240 μL, 0.868 g/mL, 1.8 mmol, 9.5 eq.) were added sequentially in one portion. The resulting mixture was stirred vigorously for 5 hours at room temperature. The reaction was quenched with saturated $NaHCO_3$ and extracted

with DCM (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 30 ⟶ 100 : 40 afforded a mixture of *tert*-butyl 5-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**333**) and *tert*-butyl 6-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-333**) (30.5 mg, 0.14 mmol, 70%) as a colorless clear oil. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

Synthesis of methyl 5-azido-5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**335**)



Following the reported procedure[95], a 20 mL round bottom flask was charged with iron(III) oxalate hexahydrate (96mg, 0.20 mmol, 3.2 eq.) and water (4 mL). The resulting suspension was left stirring for 2 hours until completely homogenous. The solution was then cooled to 0 °C and degassed by sparging with argon for 10 minutes. NaN_3 (19.2 mg, 0.30 mmol, 4.8 eq.) and EtOH (5 mL) were added sequentially in one portion. Ethanol solution (2 mL, 0.05 M) of methyl 5-phenyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**264**, 13.3 mg, 0.06 mmol, 1.0 eq.) was added with a pipette. $NaBH_4$ (13 mg, 0.63 mmol, 3.2 eq.) was added in one portion and the resulting mixture was left stirring for 5 minutes. Another portion of $NaBH_4$ was added and the resulting mixture was left stirring for 30 minutes. The reaction mixture was quenched by adding saturated aqueous ammonia (1.0 mL) and extracted with DCM : MeOH = 10 : 1 mixture (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 25 ⟶ 100 : 75 afforded methyl 5-azido-5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**335**, 6.9 mg, 0.03 mmol, 43%) as a colorless film.

^{1}H NMR (500 MHz, ^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.44 (m, 2H), 7.37 (m, 1H), 7.21 (bs, 2H), 4.71 (m, 1H), 4.19 (m, 1H), 3.83 – 3.69 (m, 1H), 3.69 – 3.56 (m, 3H), 3.34 – 3.27 (bs, 1H), 3.20 – 2.90 (m, 2H).

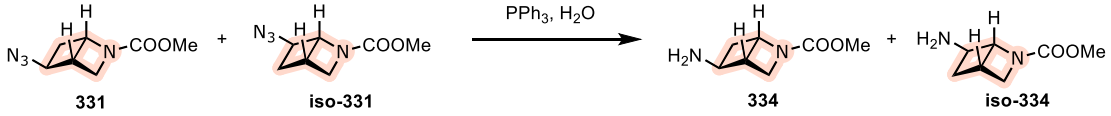
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.3, 138.1, 129.2, 128.6, 126.5, 69.4, 69.2, 57.3, 56.8, 52.4, 51.5, 41.4, 40.9, 40.8.

R_f = 0.48 (hexanes : EtOAc = 3 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2955 (w), 2102 (s), 1704 (s), 1447 (s), 1378 (s), 1233 (m), 1200 (m), 1131 (m), 705 (m).

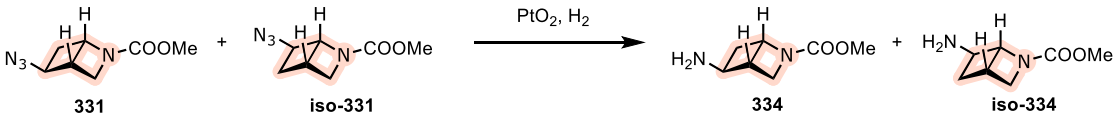
HRMS (ESI-TOF) calculated for $C_{13}H_{14}N_4O_2$+H^+: 259.1195, found: 259.1195.

Synthesis of methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**334**) and methyl 6-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-334**) via Staudinger reduction



A 10 mL round-bottom flask wash charged with a 1 : 1.9 mixture of methyl 5-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**331**) and methyl 6-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-331)** (63.6 mg, 0.349 mmol, 1.0 eq.), PPh_3 (109.4 mg, 0.417 mmol, 1.2 eq.), THF (3.5 mL, 0.1 M) and water (100 μL, 5.55 mmol, 15.9 eq.). Reaction mixture was stirred at 65 °C overnight. Solvent was removed under reduced pressure and crude product was directly loaded onto a column. Gradient elution with DCM : MeOH = 100 : 4 → 100 : 11 afforded methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**334**) and methyl 6-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-334**) (45.1 mg, 0.289 mmol, 83% combined yield) as colorless clear oils.

Synthesis of methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**334**) and methyl 6-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-334**) via catalytic hydrogenation



A 4 mL vial was charged with a 1 : 1.9 mixture of methyl 5-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**331)** and methyl 6-azido-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-331)** (42 mg, 0.23 mmol, 1.0 eq.), MeOH (1.0 mL, 0.2 M) and PtO_2 hydrate (9 mg, 0.04 mmol, 18 mol%). The resulting suspension was purged with hydrogen for 1 minute and left stirring overnight under hydrogen atmosphere (balloon). The suspension was filtered through a PTFE filter and loaded onto a column. Gradient elution with DCM : MeOH = 100 : 2 → 100 : 10 afforded methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**334**) and methyl 6-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-334**) (37 mg, 0.23 mmol, quant. combined yield) as colorless clear oils.

Methyl 6-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-334**)

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.27 – 4.10 (m, 2H), 3.87 (d, *J* = 8.3 Hz, 1H), 3.77 – 3.60 (m, 4H), 2.84 (qd, *J* = 7.6, 2.5 Hz, 1H), 2.53 (ddd, *J* = 13.4, 6.9, 2.8 Hz, 1H), 2.00 (m, 1H), 1.77 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.3, 156.1, 70.9, 70.2, 57.3, 56.4, 54.7, 54.1, 52.2, 36.5, 36.3, 27.2.

R_f = 0.39 (DCM : MeOH = 10 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3353 (bs), 2956 (m), 2881 (w), 1695 (s), 1456 (s), 1389 (s), 1200 (w), 1161 (w), 1128 (w).

HRMS (ESI-TOF) calculated for $C_7H_{12}N_2O_2$+Na^+: 179.0791, found: 179.0792.

Methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**334**)

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.54 (bs, 1H), 4.27 – 4.20 (m, 1H), 3.97 – 3.90 (m, 1H), 3.78 (m, 1H), 3.66 (s, 3H), 2.75 (m, 1H), 2.64 (bs, 1H), 2.21 (bs, 2H), 2.14 (m, 1H).

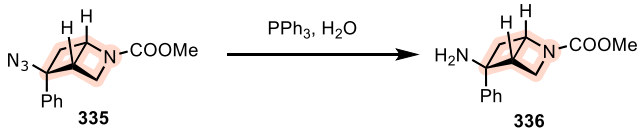
^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.6, 156.5, 59.5, 59.0, 55.5, 54.6, 53.7, 52.3, 41.6, 40.7, 40.5.

R_f = 0.19 (DCM : MeOH = 10 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3351 (bs), 2958 (m), 2883 (w), 1691 (s), 1458 (m), 1388 (m), 1199 (w), 1133 (w).

HRMS (ESI-TOF) calculated for $C_7H_{12}N_2O_2$+Na^+: 179.0971, found: 179.0792.

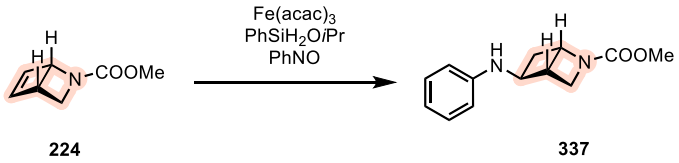
Synthesis of methyl 5-amino-5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**336**)



A 4 mL vial was charged with methyl 5-azido-5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**335**, 9.8 mg, 0.04 mmol, 1.0 eq), PPh_3 (19.9 mg, 0.08 mmol, 2.0 eq.), THF (0.4 mL) and water (40 μL). Reaction mixture was stirred at 70 °C overnight. Solvent was removed under reduced pressure and crude product was directly loaded onto a column. Gradient elution with DCM : MeOH = 100 : 2 ⟶ 100 : 10 afforded methyl 5-amino-5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**336**, 3.9 mg, 0.01 mmol, 44%) as colorless film.

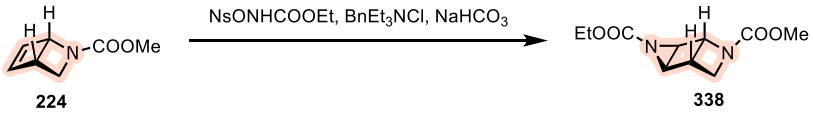
^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.37 (m, 2H), 7.27 (m, 1H), 7.20 (m, 2H), 4.71 (m, 1H), 4.14 (m, 1H), 3.76 – 3.55 (m, 4H), 3.19 – 2.93 (m, 2H), 2.64 (m, 1H), 2.02 (bs, 2H).

General procedure for hydroamination



A 4 mL vial was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 13.9 mg, 0.1 mmol, 1.0 eq.), $Fe(acac)_3$ (3–15 mol%), nitrosobenzene (1–5 eq.) and solvent mixture (0.2–1 mL, 0.1–0.5 M). Isopropoxy(phenylsilane) (2–4.5 eq.) was added in one portion and the resulting mixture was stirred at room temperature overnight. The solvent mixture was removed under reduced pressure and the residue was loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 40 afforded methyl 5-(phenylamino)-2-azabicyclo[2.2.0]hexane-2-carboxylate **337** as a colorless film.

Synthesis of 3-ethyl 6-methyl 3,6-diazatricyclo[3.2.0.0^{2,4}]heptane-3,6-dicarboxylate (**338**)



A 20 mL vial was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 100.0 mg, 0.719 mmol, 1.0 eq.), DCM (1.4 mL), $BnEt_3NCl$ (34.0 mg, 0.150 mmol, 21 mol%) and ethyl (((4-nitrophenyl)sulfonyl)oxy)carbamate (625.1 mg, 2.15 mmol, 3.0 eq.). The stirring rate was set to 1000 rpm. The resulting solution was cooled to 0 °C. Aqueous solution (4.2 mL) of $NaHCO_3$ (364.0 mg, 4.33 mmol, 6.0 eq.) was added dropwise with a syringe pump over 4 hours at 0 °C. Cooling bath was removed, and the resulting mixture was left to slowly warm to room temperature. The reaction mixture was then partitioned between DCM (20 ml) and saturated aqueous $NaHCO_3$. The organic

phase was separated, and the aqueous phase was extracted with DCM two more times (20 mL each). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : toluene : EtOAc = 75 : 25 : 40 ⟶ 75 : 25 : 60 afforded 3-ethyl 6-methyl 3,6-diazatricyclo[3.2.0.02,4]heptane-3,6-dicarboxylate (**338,** 57.4 mg, 0.254 mmol) and 54.1 mg recovered starting material. The latter was resubjected to the same reaction conditions to give 3-ethyl 6-methyl 3,6-diazatricyclo[3.2.0.$0^{2,4}$]heptane-3,6-dicarboxylate as a slightly yellow viscous oil (**SI-2,** 72.3 mg, 0.320 mmol, 44%, 2 cycles).

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 4.48 (m, 1H), 4.23 – 4.12 (m, 3H), 3.94 (d, *J* = 8.9 Hz, 2H), 3.71 (s, 3H), 3.62 (m, 1H), 3.39 (dd, *J* = 3.5, 2.1 Hz, 1H), 3.01 (dd, *J* = 6.6, 3.0 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 2H).

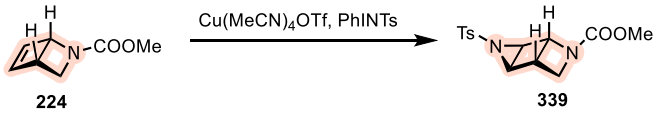
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 159.7, 156.5, 66.1, 65.7, 62.8, 52.6, 50.0, 49.3, 49.3, 40.7, 40.0, 39.9, 37.7, 14.6.

R_f = 0.49 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2982 (m), 2892 (w), 1711 (s), 1452 (m), 1372 (s), 1271 (m), 1186 (m), 1154 (w), 769 (w).

HRMS (ESI-TOF) calculated for $C_{10}H_{14}N_2O_4$+H^+: 227.1032, found: 227.1033.

Synthesis of methyl 3-tosyl-3,6-diazatricyclo[3.2.0.$0^{2,4}$]heptane-6-carboxylate (**339**)

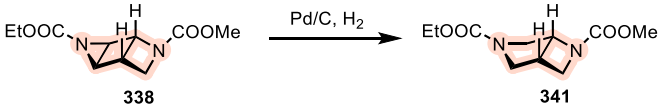


224 339

A 4 mL vial was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 51.5 mg, 0.37 mmol, 1.0 eq.) and PhINTs (138.2 mg, 0.37 mmol, 1.0 eq.). The vial was evacuated and refilled with nitrogen 3 times. Dry MeCN (0.4 mL, 0.9 M) and $[Cu(MeCN)_4]OTf$ (37.7 mg, 0.10 mmol, 27 mol%). Were added in one portion and the resulting mixture was left stirring overnight. The mixture was then filtered through a pad of silica with ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 70 afforded methyl 3-tosyl-3,6-diazatricyclo[3.2.0.$0^{2,4}$]heptane-6-carboxylate (**339**, 38.4 mg, 0.13 mmol, 34%).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 4.50 (bs, 1H), 4.17 – 4.11 (m, 1H), 3.97 – 3.92 (m, 2H), 3.88 – 3.74 (m, 1H), 3.69 (s, 3H), 3.05 – 2.98 (m, 1H), 2.45 (s, 3H).

Synthesis of 3-ethyl 6-methyl-3,6-diazabicyclo[3.2.0]heptane-3,6-dicarboxylate (**341**)



338 341

To a stirred solution of 3-ethyl 6-methyl 3,6-diazatricyclo[3.2.0.$0^{2,4}$]heptane-3,6-dicarboxylate (**338**, 15.0 mg, 0.066 mmol, 1.0 eq.) in MeOH (1.5 mL, 0.04 M) was added palladium on carbon (10% w/w, 15.0 mg, 10 mol%). The suspension was purged with hydrogen gas for 1 minute and left stirring for 16 hours under hydrogen atmosphere (balloon). The reaction mixture was filtered through a pad of celite

and concentrated under reduced pressure to afford 3-ethyl 6-methyl nahco33,6-diazabicyclo[3.2.0]heptane-3,6-dicarboxylate (**341,** 10.9 mg, 0.048 mmol, 72%) as a colorless film.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 4.70 (bs, 1H), 4.16 (q, *J* = 6.6 Hz, 2H), 4.08 (t, *J* = 8.2 Hz, 2H), 3.84 (m, 1H), 3.65 (s, 3H), 3.60 (m, 1H), 3.21 (dd, *J* = 11.9, 6.7 Hz, 1H), 3.07 (m, 2H), 1.27 (t, *J* = 7.0 Hz, 3H).

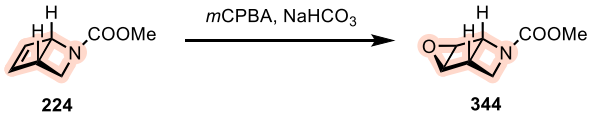
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 155.9, 66.1, 65.6, 65.2, 61.5, 54.0, 53.2, 52.3, 51.0, 50.3, 33.8, 32.9, 14.8.

R_f = 0.45 (EtOAc; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2957 (w), 2883 (w), 1698 (s), 1451 (m), 1427 (w), 1383 (m), 1235 (w), 1135 (w), 1027 (w), 770 (w).

HRMS (ESI-TOF) calculated for $C_{10}H_{16}N_2O_4+H^+$: 229.1188, found: 229.1190.

Synthesis of methyl 3-oxa-6-azatricyclo[3.2.0.02,4]heptane-6-carboxylate (**344**)



224 **344**

A 4 mL vial was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 55.6 mg, 0.400 mmol, 1.0 eq.), DCM (2.0 mL, 0.2 M) and $NaHCO_3$ (201.6 mg, 2.40 mmol, 6.0 eq.). The resulting suspension was cooled to 0 °C in an ice bath and purified *m*CPBA[102] (207.2 mg, 1.20 mmol, 3.0 eq.) was added in one portion. The ice bath was removed and the resulting mixture left stirring for 16 hours at room temperature, during which the mixture solidified. The mixture was filtered through a pad of celite, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : toluene : EtOAc = 75 : 25 : 30 ⟶ 75 : 25 : 50 afforded methyl 3-oxa-6-azatricyclo[3.2.0.0^{2,4}]heptane-6-carboxylate (**344**, 41.4 mg, 0.267 mmol, 67%) as a colorless clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 4.46 (m, 1H), 4.24 (m, 1H), 4.12 – 4.02 (m, 2H), 3.90 (d, *J* = 7.7 Hz, 1H), 3.69 (s), 3.11 – 2.80 (m, 1H).

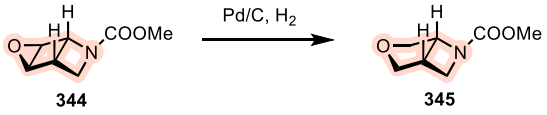
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 156.8, 156.7, 68.0, 67.6, 56.0, 55.9, 52.6, 48.6, 47.9, 40.0.

R_f = 0.47 (hexanes : EtOAc = 1 : 1; cerium molybdate)

IR (ATR-FTIR, cm^{-1}): 2958 (w), 2891(w), 1706 (s), 1453 (s), 1386 (s), 1201 (w), 1121 (m), 981 (m), 771 (m).

HRMS (ESI-TOF) calculated for $C_7H_9NO_3+H^+$: 156.0661, found: 156.0662.

Synthesis of methyl 3-oxa-6-azabicyclo[3.2.0]heptane-6-carboxylate (**345**)



344 **345**

A 4 mL vial was charged with methyl 3-oxa-6-azatricyclo[3.2.0.0^{2,4}]heptane-6-carboxylate (**344**, 41.4 mg, 0.267 mmol, 1.0 eq.), MeOH (2.5 mL, 0.11 M) and palladium on carbon (26.6 mg, 10% w/w). The

resulting suspension was purged with hydrogen for 2 minutes and left stirring under hydrogen atmosphere (balloon) for 2 hours. The reaction mixture was filtered through a pad of celite and solvent was removed under reduced pressure to yield methyl 3-oxa-6-azabicyclo[3.2.0]heptane-6-carboxylate (**345,** 30.6 mg, 0.195 mmol, 73%) as a colorless clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 4.75 (dm, 1H), 4.24 (m, 1H), 4.01 (m, 2H), 3.64 (s, 4H), 3.47 (dd, *J* = 9.8, 5.0 Hz, 1H), 3.32 (d, *J* = 2.5 Hz, 1H), 3.08 (p, *J* = 5.9, 5.1 Hz, 1H).

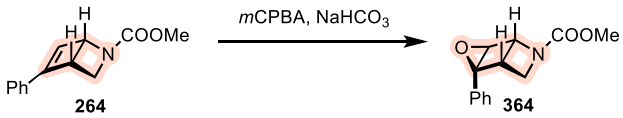
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 155.7, 71.9, 71.8, 71.4, 66.8, 66.2, 53.5, 52.5, 52.2, 34.7.

R_f = 0.47 (EtOAc; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2957 (m), 2854 (w), 1707 (s), 1452 (s), 1388 (s), 1364 (w), 1190 (w), 1077 (w), 912 (w).

HRMS (ESI-TOF) calculated for $C_7H_{11}NO_3$+H^+: 158.0817, found: 158.0819.

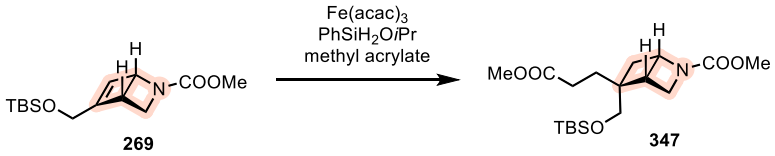
Synthesis of methyl 2-phenyl-3-oxa-6-azatricyclo[3.2.0.0^{2,4}]heptane-6-carboxylate (**346**)



A 4 mL vial was charged with methyl 5-phenyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**264**, 21.8 mg, 0.10 mmol, DCM (2.0 mL, 0.2 M) and $NaHCO_3$ (50.4 mg, 0.60 mmol, 6.0 eq.). The resulting suspension was cooled to 0 °C in an ice bath and purified *m*CPBA[102] (51.8 mg, 0.30 mmol, 3.0 eq.) was added in one portion. The ice bath was removed and the resulting mixture left stirring overnight, during which the mixture solidified. The mixture was loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 40 afforded methyl 3-oxa-6-azatricyclo[3.2.0.0^{2,4}]heptane-6-carboxylate (**346**, 15.4 mg, 0.07 mmol, 66%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.37 (m, 3H), 7.22 (m, 2H), 4.72 (m, 1H), 4.56 (m, 1H), 4.25 (m, 1H), 4.02 (bs, 1H), 3.76 – 3.65 (m, 3H), 3.37 (m, 1H).

Synthesis of methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(3-methoxy-3-oxopropyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**347**)



A 4 mL vial was charged with methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**269**, 28.3 mg, 0.10 mmol, 1.0 eq.), $Fe(acac)_3$ (5.3 mg, 0.015 mmol, 15 mol%), isopropanol (0.32 mL), EtOAc (0.32 mL), methyl acrylate (25 μL, 0.950 g/mL, 0.28 mmol, 2.8 eq.) and isopropoxy(phenyl)silane (100 μL, 0.926 g/mL, 0.56 mmol, 5.6 eq.). The resulting mixture was stirred at room temperature overnight. Water (50 mL) and Et_2O (50 mL) were added, and phases were separated. The organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with

hexanes : EtOAc = 100 : 10 ⟶ 100 : 50 afforded 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(3-methoxy-3-oxopropyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**347**, 17.5 mg, 0.047 mmol, 47%) as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 4.51 (m, 1H), 4.26 – 4.10 (m, 2H), 3.93 – 3.84 (m, 1H), 3.67 (bs, 6H), 3.54 (m, 1H), 2.57 (m, 1H), 2.25 (m, 2H), 2.08 – 1.86 (m, 3H), 1.80 (m, 1H), 0.86 (s, 9H), 0.05 (dm, 6H).

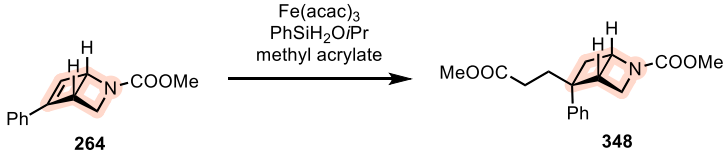
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 174.3, 156.4, 156.1, 63.8, 63.7, 58.7, 58.3, 52.2, 52.0, 51.8, 51.0, 42.0, 41.9, 37.6, 36.9, 36.3, 33.0, 28.8, 25.9, 18.3, -5.4.

R_f = 0.64 (hexanes : EtOAc = 3 : 2; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2954 (m), 2930 (m), 2888 (w), 2857 (m), 1739 (s), 1708 (s), 1449 (s), 1380 (s), 1091 (s), 936 (s), 774 (s).

HRMS (ESI-TOF) calculated for $C_{18}H_{33}NO_5Si+H^+$: 372.2206, found: 372.2203.

Synthesis of methyl 5-(3-methoxy-3-oxopropyl)-5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**348**)



264 348

A 4 mL vial was charged with methyl 5-phenyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**264**, 21.2 mg, 0.10 mmol, 1.0 eq.), $Fe(acac)_3$ (35.3 mg, 0.10 mmol, 1 eq.), isopropanol (0.5 mL), EtOAc (0.5 mL), methyl acrylate (100 μL, 0.950 g/mL, 1.1 mmol, 11.2 eq.) and isopropoxy(phenyl)silane (100 μL, 0.926 g/mL, 0.56 mmol, 5.6 eq.). The resulting mixture was stirred 4 h at room temperature then 1 h at 40 °C and finally at 60 °C overnight. After cooling to room temperature, the reaction solvent was removed, and the residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 25 ⟶ 100 : 100 afforded methyl 5-(3-methoxy-3-oxopropyl)-5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**348**, 11.5 mg, 0.038 mmol, 38%) as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.37 – 7.30 (bs, 2H), 7.21 (bs, 1H), 6.97 (bs, 2H), 4.61 (m, 1H), 4.13 (m, 1H), 3.90 – 3.74 (m, 1H), 3.63 (m, 1H), 3.57 (s, 6H), 3.06 (bs, 1H), 2.73 (dd, *J* = 42.1, 13.4 Hz, 1H), 2.56 (m, 1H), 2.14 – 1.91 (m, 4H).

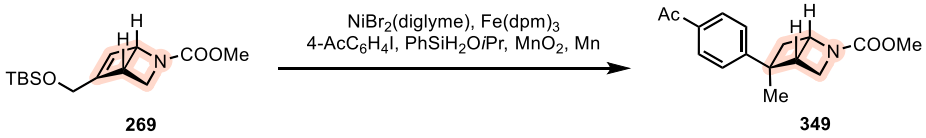
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 173.9, 156.3, 156.2, 143.3, 143.1, 128.6, 126.8, 126.7, 126.4, 57.6, 57.0, 52.7, 52.3, 52.2, 51.9, 51.8, 46.8, 46.6, 40.3, 39.9, 39.6, 39.3, 29.2.

R_f = 0.50 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2953 (w), 1736 (s), 1706 (s), 1447 (s), 1377 (s), 1199 (s), 764 (s), 705 (s).

HRMS (ESI-TOF) calculated for $C_{17}H_{21}NO4+H^+$: 304.1549, found: 304.1548.

Synthesis of methyl 5-(4-acetylphenyl)-5-methyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**349**)



269 349

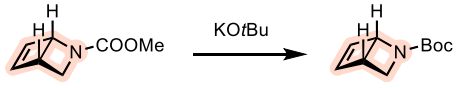
Following the reported procedure[104], an oven dried 4 mL vial was charged with methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**269**, 28.3 mg, 0.10 mmol, 1.0 eq.), $Fe(dpm)_3$ (18.2 mg, 0.03 mmol, 30 mol%), manganese powder (5.5 mg, 0.1 mmol, 1.0 eq.), $NiBr_2$(diglyme) (3.5 mg, 0.01 mmol, 10mol%) and 4-iodoacetophenone (39.0 mg, 0.16 mmol, 1.6 eq.). The reaction mixture was placed under nitrogen and DCE (0.5 mL) and NMP (0.5 mL) were added. After 1.5 h of stirring at room temperature, MnO_2 (17.5 mg, 0.20 mmol, 2.0 eq.) was added in one portion. Yellow needle was inserted through the vial cap septum and the first portion of isopropoxyphenylsilane (20 μL, 0.926 g/mL, 0.11 mmol, 1.1 eq) was added. The resulting mixture was stirred for 1 h and then the second portion of silane was added. The reaction mixture was stirred for 2 days at room temperature, filtered through a pad of celite with EtOAc and partitioned between 50 mL of EtOAc and 50 mL of water. The organic layer was separated and washed with water two more times, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 50 ⟶ 100 : 200 afforded methyl 5-(4-acetylphenyl)-5-methyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**349**, 7.7 mg, 0.03 mmol, 28%) as a slightly yellow film.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.56 (m, 1H), 4.38 – 4.32 (m, 2H), 3.71 (bs, 3H), 3.22 – 3.17 (m, 1H), 2.91 (m, 1H), 2.59 (s, 3H), 1.60 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 156.6, 156.4, 135.1, 128.8, 125.7, 59.2, 58.8, 52.3, 51.5, 43.5, 43.2, 42.8, 40.6, 27.5, 26.7.

MS (ESI-Q) calculated for $C_{16}H_{16}NO_3$+H^+: 274, found: 274.

Synthesis of *tert*-butyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**332**)



224 332

A flame dried 50 mL two-neck round bottom flask was charged with methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 505 mg, 3.6 mmol, 1.0 eq.) and THF (14 mL). The resulting solution was cooled to 0 °C in an ice bath. KO*t*Bu solution (4.0 mL, 1 M in THF, 4.0 mmol, 1.1 eq.) was canulated to the substrate solution. After the addition was complete, the ice bath was removed, and the resulting brown solution was stirred at room temperature overnight. The reaction mixture was quenched with 10% aqueous NH_4Cl and the product was extracted with EtOAc (3 x 40 mL). Combined organic phases were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Isocratic elution with hexanes : EtOAc = 100 : 15 afforded *tert*-butyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**332**, 247.3 mg, 2.6 mmol, 72%) as a colorless clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 6.45 (m, 2H), 4.75 (m, 1H), 3.88 (bs, 1H), 3.43 (bs, 1H), 3.34 (m, 1H) 1.43 (s, 9H).

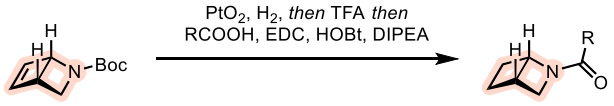
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 157.1, 143.3, 143.0, 141.0, 140.2, 79.4, 65.9, 65.0, 50.4, 49.3, 28.5.

R_f = 0.71 (hexanes : EtOAc = 4 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2976 (m), 2886 (w), 1698 (s), 1364 (s), 1149 (m), 1186 (m), 1103 (w), 761 (m).

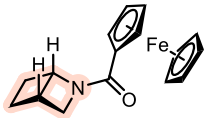
HRMS (ESI-TOF) calculated for $C_{10}H_{15}NO_2$+Na^+: 204.1000, found: 204.0999.

Synthesis of amides (**363**–**365**)



332 **363–365**

A 20 mL vial was charged with *tert*-butyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**332**, 153.9 mg, 0.85 mmol, 1.0 eq.), MeOH (8.6 mL, 0.1 M) and PtO_2 hydrate (19.4 mg, 0.085 mmol, 10 mol%). The resulting suspension was purged with hydrogen for 1 minute and left stirring for 1 hour under hydrogen atmosphere (balloon). The suspension was then filtered through a pad of celite, concentrated under reduced pressure and redissolved in DCM (3.6 mL). The resulting solution was cooled to 0 °C in an ice bath and degassed by sparging with argon for 2 minutes. TFA (0.9 mL, 1.490 g/mL, 11.7 mmol, 14 eq.) was added via syringe in one portion. The cooling bath was removed, and the reaction mixture was stirred for 15 minutes at room temperature. Solvent was removed under reduced pressure. Excess TFA was azeotropically removed with MeOH and DCM. Crude residue was redissolved in DMF (2.1 mL). A 4 mL vial was charged with 0.7 mL of the DMF substrate stock solution, carboxylic acid (0.31 mmol, 1.1 eq.), HOBt hydrate (53.4 mg, 0.312 mmol), DIPEA (170 μL, 0.742 g/mL, 0.976 mmol) and additional DMF (0.7 mL). The resulting solution was cooled to 0 °C in an ice bath and EDC·HCl (60.0 mg, 0.313 mmol, 1.1 eq.) was added in one portion. The cooling bath was removed, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with EtOAc (50 mL), washed with 1 M aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$ and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 100 ⟶ pure EtOAc afforded the corresponding amides (**363**–**365**).



363

Prepared from 70.8 mg ferrocenecarboxylic acid.
50.1 mg, 0.17 mmol, 61% yield over 3 steps, orange oil that solidified on standing.

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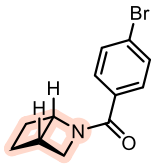
^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 4.90 (dm 1H), 4.72 (m, 1H), 4.64 – 4.12 (m, 10H), 3.01 (bs, 1H), 2.78 – 2.62 (m, 1H), 2.50 (m, 2H), 2.28 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 70.6, 70.6, 70.4, 70.3, 70.0, 69.8, 69.7, 69.6, 69.5, 68.9, 65.7, 63.7, 61.4, 57.2, 31.6, 31.5, 30.2, 28.9, 26.5, 25.6. *Carbonyl carbon peak was not observed.*

R_f = 0.32 (EtOAc; UV)

IR (ATR-FTIR, cm^{-1}): 3093 (w), 2937 (w), 2872 (w), 1611(s), 1475 (m), 1462 (s), 1407 (s), 1368 (w), 1106 (w), 762 (m).

HRMS (ESI-TOF) calculated for $C_{16}H_{17}NOFe+H^+$: 296.0738, found: 296.0744.



364

Prepared from 61.9 mg 4-bromobenzoic acid.
57.7 mg, 0.22 mmol, 77% yield over 3 steps, white solid.

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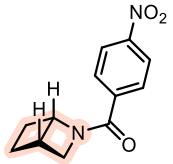
^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.57 – 7.44 (m, 4H), 4.83 (m, 1H), 4.67 – 4.45 (m, 1H), 4.26 (m, 1H), 3.09 – 2.93 (m, 1H), 2.64 (m, 1H), 2.50 (m, 2H), 2.43 – 2.19 (m, 1H).

MS (ESI-Q) calculated for $C_{12}H_{12}NOBr+H^+$: 266, found: 266.



365

Prepared from 51.5 mg 4-nitrobenzoic acid.
46.2 mg, 0.20 mmol, 71% yield over 3 steps, white solid.

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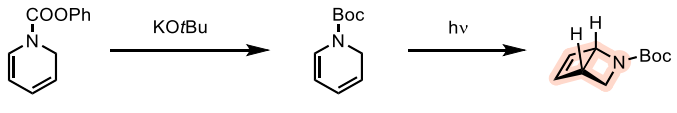
^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 8.27 (m, 2H), 7.79 (m, 2H), 4.85 (m, 1H), 4.68 – 4.51 (m, 1H), 4.28 (m, 1H), 3.12 – 2.98 (m, 1H), 2.67 (m, 1H), 2.60 – 2.47 (m, 1H), 2.33 (m, 2H).

MS (ESI-Q) calculated for $C_{12}H_{12}N_2O_3+H^+$: 233, found: 233.

Alternative synthesis of *tert*-butyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**332**)



367 **368** **332**

A flame dried 50 mL two-neck round bottom flask was charged with phenyl pyridine-1(2H)-carboxylate (**367**, 500 mg, 2.48 mmol, 1.0 eq.)[108] and anhydrous THF (4.0 mL) under nitrogen atmosphere. The resulting solution was cooled to -78 °C using an acetone/dry ice bath. KO*t*Bu solution (1.0 M in THF, 7.5 mL, 7.50 mmol, 3.0 eq.) was slowly added and the resulting mixture was stirred for 1.5 hours at -78°C. The reaction mixture was quenched at the same temperature with 10% aqueous NH_4Cl and the product was extracted with Et_2O (50 mL). The organic phase was separated, washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 15 afforded *tert*-butyl pyridine-1(2H)-carboxylate (**368**, 430 mg, 2.37 mmol, 96%) as a colorless clear oil.

Acetone solution (24 mL, 0.1 M) of *tert*-butyl pyridine-1(2H)-carboxylate (**368**, 430 mg, 2.37 mmol) was degassed by sparging with argon for 2 minutes in an ultrasonic bath. Degassed solution was then

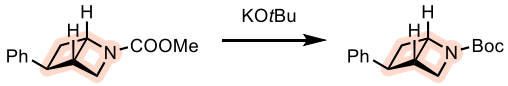
irradiated in a Rayonet photoreactor equipped with 350 nm lamps for 4 days. Solvent was removed and crude product was directly loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 15 afforded methyl *tert*-butyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**332**, 127 mg, 0.70 mmol, 29%) as a colorless clear oil. The spectral data matches the product from the reaction between **224** and KO*t*Bu.

Characterization data for *tert*-butyl pyridine-1(4H)-carboxylate (**366**)

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 6.68 (m, 2H), 4.94 – 4.71 (m, 2H), 2.83 (tt, *J* = 3.5, 1.8 Hz, 2H), 1.49 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 150.4, 124.2, 123.7, 105.7, 105.0, 81.7, 28.3, 22.6.

Synthesis of *tert*-butyl 5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**369**)



321 **369**

A 20 mL vial was charged with methyl 5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**321**, 97.2 mg, 0.447 mmol, 1.0 eq.) and THF (1.3 mL) under nitrogen atmosphere. The resulting solution was cooled to 0 °C in an ice bath and KO*t*Bu solution (0.90 mL, 1.0 M, 0.900 mmol, 2.0 eq.) was added in one portion via syringe. The ice bath was removed, and the reaction mixture was left stirring overnight at room temperature. The reaction mixture was partitioned between 10% aqueous NH_4Cl and Et_2O. The organic phase was separated, dried over $MgSO_4$, concentrated under reduced pressure, and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 20 afforded *tert*-butyl 5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**369**, 87.9 mg, 0.339 mmol, 76%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.33 (m, 2H), 7.22 (m, 3H), 4.62 (m, 1H), 4.32 (m, 1H), 4.09 (m, 1H), 3.77 (m, 1H), 2.98 – 2.92 (m, 1H), 2.88 (m, 1H), 2.56 (m, 1H), 1.48 (s, 9H).

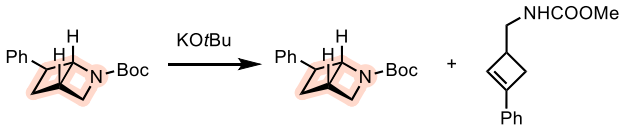
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 155.9, 145.4, 128.7, 126.56, 126.4, 79.5, 61.2, 60.5, 58.2, 56.7, 45.4, 38.4, 37.9, 28.7.

R_f = 0.63 (hexanes : EtOAc = 4 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2975 (w), 2934 (w), 2879 (w), 1698 (s), 1391 (s), 1180 (w), 1151 (m), 1128 (m), 871 (w), 773 (w), 752 (w).

HRMS (ESI-TOF) calculated for $C_{16}H_{21}NO_2$+Na^+: 282.1470, found: 282.1482.

Synthesis of *tert*-butyl 6-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-369**)



iso-321 **iso-369** **370**

A 20 mL vial was charged with methyl 6-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-321**, 129.7 mg, 0.597 mmol, 1.0 eq.) and THF (1.8 mL) under nitrogen atmosphere. The resulting solution

was cooled to 0 °C in an ice bath and KO*t*Bu solution (1.20 mL, 1.0 M, 1.20 mmol, 2.0 eq.) was added in one portion via syringe. The ice bath was removed, and the reaction mixture was left stirring overnight at room temperature. The reaction mixture was partitioned between 10% aqueous NH_4Cl and Et_2O. The organic phase was separated, dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 5 ⟶ 100 : 15 afforded *tert*-butyl 6-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-369**, 91.4 mg, 0.352 mmol, 59%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.39 – 7.19 (m, 5H), 4.54 – 4.41 (m, 1H), 4.33 – 4.28 (m, 1H), 4.16 – 4.03 (m, 1H), 3.89 – 3.75 (m, 1H), 2.90 (m, 1H), 2.68 – 2.62 (m, 1H), 1.48 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 155.6, 143.4, 128.7, 128.6, 126.5, 126.4, 79.6, 69.9, 69.2, 58.0, 56.7, 47.3, 46.8, 32.8, 32.6, 28.7, 28.3, 28.1.

R_f = 0.64 (hexanes : EtOAc = 4 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2974 (w), 2936 (w), 2879 (w), 1695 (s), 1388 (s), 1365 (m), 748 (w), 699 (w).

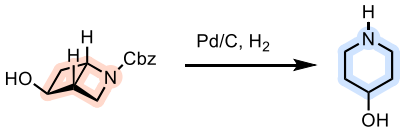
HRMS (ESI-TOF) calculated for $C_{16}H_{21}NO_2$+Na^+: 282.1470, found: 282.1472.

Methyl ((3-phenylcyclobut-2-en-1-yl)methyl)carbamate (**370**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 4H), 7.32 – 7.26 (m, 1H), 4.86 (bs, 1H), 3.70 (s, 3H), 3.40 (ddt, *J* = 25.3, 13.0, 6.4 Hz, 2H), 3.06 – 2.98 (m, 1H), 2.93 (dd, *J* = 13.0, 4.5 Hz, 1H), 2.46 (d, *J* = 13.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 146.7, 134.4, 128.5, 128.1, 127.8, 124.7, 52.2, 44.6, 38.6, 32.2.

Benzyloxycarbonyl deprotection attempts

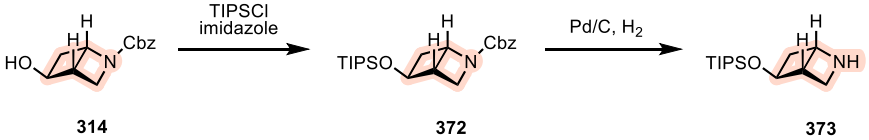


314 **371**

A 4 mL vial was charged with benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**314**, 10.0 mg, 0.04 mmol, 1.0 eq.), MeOH (0.5 mL, 0.1 M) and Pd/C (10.0 mg, 10% w/w, 0.01 mmol, 20 mol%). The resulting suspension was purged with hydrogen for 1 minute and left stirring overnight under hydrogen atmosphere (balloon). The suspension was filtered through a PTFE filter and concentrated under reduced pressure. ^{1}H NMR analysis of the residue showed exclusive formation of piperidin-4-ol (**371**).

^{1}H NMR (400 MHz, CD_3OD) δ 3.68 (tt, *J* = 9.0, 4.1 Hz, 1H), 3.09 – 3.01 (m, 2H), 2.62 (ddd, *J* = 13.2, 10.4, 3.0 Hz, 2H), 1.92 – 1.81 (m, 2H), 1.44 (dddd, *J* = 13.2, 10.4, 9.3, 4.0 Hz, 2H).

Successful benzyloxycarbonyl deprotection



314 372 373

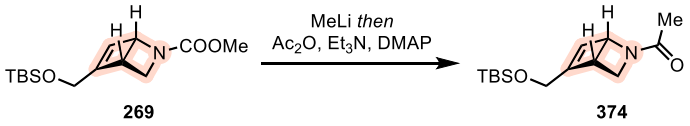
A 4 mL vial was charged with benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**314**, 100.0 mg, 0.43 mmol, 1.0 eq.), DCM (2 mL, 0.2 M), imidazole (59.0 mg, 0.87 mmol, 2.0 eq.) and TIPSCl (190 μL, 0.901 g/mL 0.89 mmol, 2.1 eq.). The resulting mixture was left stirring overnight, quenched with saturated $NaHCO_3$ and extracted with DCM (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 4 → 100 : 8 afforded benzyl 5-((triisopropylsilyl)oxy)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**372**, 148.1 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 5.10 (bs, 1H), 4.58 (td, *J* = 5.6, 1.7 Hz, 2H), 4.25 (dd, *J* = 9.0, 7.0 Hz, 1H), 3.89 (dd, *J* = 9.0, 2.1 Hz, 1H), 2.81 (m, 2H), 2.35 (m, 1H), 1.16 – 0.92 (m, 21H).

A 4 mL vial was charged with benzyl 5-((triisopropylsilyl)oxy)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**372**, 10.0 mg, 0.03 mmol, 1.0 eq.), MeOH (0.5 mL, 0.1 M) and Pd/C (10.0 mg, 10% w/w, 0.01 mmol, 27 mol%). The resulting suspension was purged with hydrogen for 1 minute and left stirring overnight under hydrogen atmosphere (balloon). The suspension was filtered through a PTFE filter and concentrated under reduced pressure to yield 5-((triisopropylsilyl)oxy)-2-azabicyclo[2.2.0]hexane (**373**, 9.0 mg, 0.03 mmol, quant.)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (bs, 1H), 4.76 (bs, 1H), 4.55 (bs, 1H), 4.28 (bs, 1H), 3.85 (m, 1H), 3.31 – 3.23 (m, 1H), 2.97 (bs, 1H), 2.53 (m, 1H), 1.03 (m, 21H).

Synthesis of 1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-en-2-yl)ethan-1-one **374**)



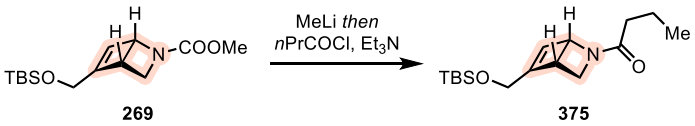
269 374

A flame dried 50 mL two-neck round bottom flask was charged with methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**269**, 100 mg, 0.35 mmol, 1.0 eq.) and anhydrous THF (3.5 mL, 0.1 M) under nitrogen atmosphere. The resulting solution was cooled to -20 °C and MeLi solution (0.75 mL, 1.6 M in Et_2O, 1.2 mmol, 3.4 eq.) was slowly added. The resulting mixture was warmed up to -10 °C and left stirring for 15 minutes at the same temperature. Afterwards, it was quenched with water and extracted with EtOAc (50 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was redissolved in DCM (3.5 mL) and the resulting solution was cooled to 0 °C in an ice bath. Triethylamine (100 μL, 0.742 g/mL, 0.73 mmol, 2.1 eq.), acetic anhydride (70 μL, 1.082 g/mL, 0.74 mmol, 2.1 eq. and 1 crystal of DMAP were added sequentially in one portion. The ice bath was removed, and the resulting mixture was left to warm up to room temperature. Afterwards, 50 mL saturated aqueous $NaHCO_3$ were added, and the aqueous phase was extracted with DCM (3 x 20 mL). Combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and loaded

onto a column. Gradient elution with hexanes : EtOAc = 100 : 100 ⟶ pure EtOAc afforded 1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-en-2-yl)ethan-1-one (**374**, 52.3 mg, 55% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.35 (m, 1H), 4.97 – 4.75 (m, 1H), 4.24 (m, 2H), 3.97 (m, 1H), 3.66 – 3.53 (m, 1H), 3.47 – 3.35 (m, 1H), 1.88 (m, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

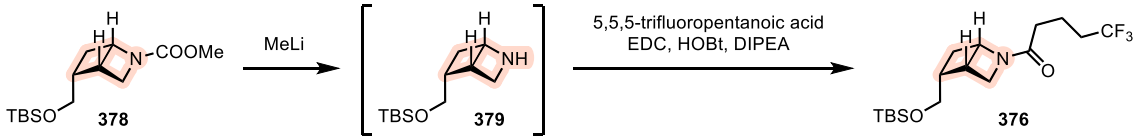
Synthesis of 1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-en-2-yl)butan-1-one (**375**)



269 **375**

A flame dried 50 mL two-neck round bottom flask was charged with methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**269**, 100 mg, 0.35 mmol, 1.0 eq.) and anhydrous THF (3.5 mL, 0.1 M) under nitrogen atmosphere. The resulting solution was cooled to -20 °C and MeLi solution (0.75 mL, 1.6 M in Et_2O, 1.2 mmol, 3.4 eq.) was slowly added. The resulting mixture was warmed up to -10 °C and left stirring for 15 minutes at the same temperature. Afterwards, it was quenched with water and extracted with EtOAc (50 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was redissolved in DCM (3.5 mL) and the resulting solution was cooled to 0 °C in an ice bath. Triethylamine (100 μL, 0.742 g/mL, 0.73 mmol, 2.1 eq.) and butyryl chloride (70 μL, 1.0 g/mL, 0.74 mmol, 1.9 eq.). The ice bath was removed, and the resulting mixture was left to warm up to room temperature. Afterwards, 50 mL saturated aqueous $NaHCO_3$ were added, and the aqueous phase was extracted with DCM (3 x 20 mL). Combined organic phases were dried over Na_2SO_4, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 50 ⟶ 100 : 100 1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-en-2-yl)butan-1-one (**375**, 49.8 mg, 48% over 2 steps).

Synthesis of 1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hexan-2-yl)-5,5,5-trifluoropentan-1-one (**376**)



378 **379** **376**

A flame dried 50 mL two-neck round bottom flask was charged with methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**378**, 200 mg, 0.7 mmol, 1.0 eq.) and anhydrous THF (7 mL, 0.1 M) under nitrogen atmosphere. The resulting solution was cooled to -20 °C and MeLi solution (1.5 mL, 1.6 M in Et_2O, 2.4 mmol, 3.4 eq.) was slowly added. The resulting mixture was warmed up to -10 °C and left stirring for 15 minutes at the same temperature. Afterwards, it was quenched with water and extracted with EtOAc (50 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield crude amine **379**.

A 25 mL round bottom flask was charged with 5,5,5-trifluoropentanoic acid (90 μL, 1.293 g/mL, 0.75 mol, 1.1 eq.) and DCM (3 mL). The resulting solution was cooled to 0 °C in an ice bath. HOBt hydrate (117.8 mg, 0.77 mmol, 1.1 eq.), DIPEA (130 μL, 0.742 g/mL, 0.77 mmol, 1.1 eq.) and EDC (147.6 mg, 0.77 mmol, 1.1 eq.) were added sequentially in one portion. After stirring for 20 minutes at 0 °C, solution of crude amine **379** in DCM (4 mL) was added as well as another portion of DIPEA (130 μL, 0.742 g/mL, 0.77 mmol, 1.1 eq.). The ice bath was removed, and the reaction mixture was left stirring overnight. The reaction mixture was partitioned between EtOAc (50 mL) and 0.5 M aqueous HCl (50 mL). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (50 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 60 afforded 1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hexan-2-yl)-5,5,5-trifluoropentan-1-one (**376**, 112.2 mg, 0.31 mmol, 44% over 2 steps) as a colorless clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 4.68 – 4.56 (m, 1H), 4.45 – 4.10 (m, 2H), 3.90 – 3.71 (m, 2H), 3.10 – 2.99 (m, 1H), 2.85 (m, 1H), 2.59 (m, 1H), 2.22 – 1.82 (m, 7H), 0.86 (dm, 9H), 0.04 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 171.1, 170.7, 127.2 (q, *J* = 276.5 Hz), 63.1, 63.0, 60.6, 59.4, 52.0, 49.5, 35.6, 35.4, 33.1 (q, *J* = 28.1 Hz), 32.1, 32.0, 31.9, 31.0, 30.0, 29.8, 26.0, 18.4, 17.4 (m), -5.17, -5.22, -5.26.

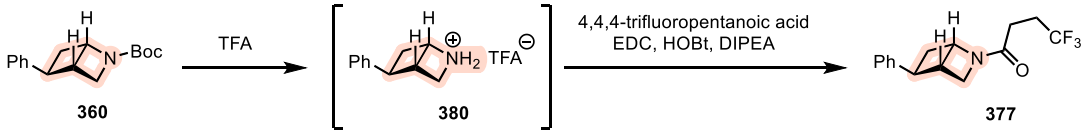
^{19}F NMR (565 MHz, $CDCl_3$, rotamers) δ -66.0 (m).

R_f = 0.50 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2932 (m), 2858 (w), 1651 (s), 1443 (m), 1256 (s), 1134 (s), 1098 (s), 836 (s), 777 (m).

HRMS (ESI-TOF) calculated for $C_{17}H_{30}NO_2SiF_3+H^+$: 366.2076, found: 366.2071.

Synthesis of 4,4,4-trifluoro-1-(5-phenyl-2-azabicyclo[2.2.0]hexan-2-yl)butan-1-one (**377**)



A 4 mL vial was charged with *tert*-butyl 5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**360**, 80.5 mg, 0.310 mmol, 1.0 eq.) and DCM (1.2 mL). The resulting solution was cooled to 0 °C in an ice bath and degassed by purging with argon for 1 minute. TFA (300 μL, 1.490 g/mL, 3.92 mmol, 12.6 eq.) was added in one portion. The ice bath was removed, and the resulting mixture was left stirring at room temperature for 15 minutes. Solvent was removed under reduced pressure. Excess TFA was azeotropically removed with MeOH and DCM (1 mL each). The crude ammonium salt **380** was redissolved in DMF (1.5 mL) and the resulting solution was cooled to 0 °C. DIPEA (190 μL, 0.742 g/mL, 1.09 mmol, 3.5 eq.), HOBt hydrate (55.3 mg, 0.323 mmol, 1.0 eq.), 4,4,4-trifluorobutyric acid (51.2 mg, 0.360 mmol, 1.2 eq.) and EDC·HCl (69.0 mg, 0.360 mmol, 1.2 eq.) were added sequentially in one portion. The ice bath was removed, and the resulting mixture was left stirring overnight at room temperature. The reaction mixture was diluted with EtOAc (50 mL) and quenched with 0.5 M HCl (50 mL). The organic phase was separated, washed with saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified with automated reverse phase liquid chromatography. Gradient elution with H_2O : MeCN = 50 : 50 ⟶ 0 : 100 afforded 4,4,4-trifluoro-1-(5-

phenyl-2-azabicyclo[2.2.0]hexan-2-yl)butan-1-one (**377**, 59.5 mg, 0.210 mmol, 68%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.35 (m, 2H), 7.26 – 7.20 (m, 3H), 4.80 (m, 1H), 4.57 – 4.18 (m, 2H), 3.80 (m, 1H), 3.08 (m, 1H), 2.93 – 2.25 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 169.9, 169.6, 144.7, 144.4, 128.8, 128.8, 126.7, 126.7, 126.5, 126.5, 61.3, 60.2, 58.5, 56.4, 45.5, 45.1, 38.3, 38.0, 37.5, 29.2 (q, *J* = 29.7 Hz), 29.2 (q, *J* = 29.6 Hz), 24.5 (q, *J* = 2.9 Hz), 24.2 (q, *J* = 3.0 Hz)

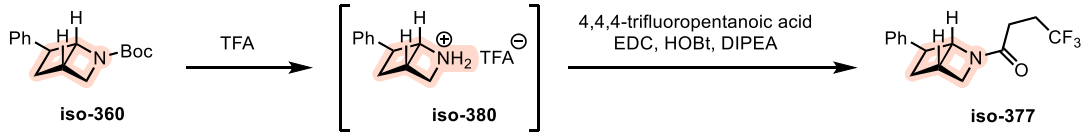
^{19}F NMR (471 MHz, $CDCl_3$) δ -66.7 (m).

R_f = 0.54 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2946 (w), 2878 (w), 1652 (s), 1446 (s), 1383 (m), 1251 (w), 1136 (m), 1106 (m), 979 (w), 753 (w), 700 (w).

HRMS (ESI-TOF) calculated for $C_{15}H_{16}NOF_3$+H^+: 284.1262, found: 284.1264.

Synthesis of 4,4,4-trifluoro-1-(6-phenyl-2-azabicyclo[2.2.0]hexan-2-yl)butan-1-one (**iso-377**)



A 4 mL vial was charged with *tert*-butyl 6-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-360**, 78.1 mg, 0.301 mmol, 1.0 eq.) and DCM (1.2 mL). The resulting solution was cooled to 0 °C in an ice bath and degassed by purging with argon for 1 minute. TFA (300 μL, 1.490 g/mL, 3.92 mmol, 13.0 eq.) was added in one portion. The ice bath was removed, and the resulting mixture was left stirring at room temperature for 15 minutes. Solvent was removed under reduced pressure. Excess TFA was azeotropically removed with MeOH and DCM (1 mL each). The crude ammonium salt **iso-380** was redissolved in DMF (1.5 mL) and the resulting solution was cooled to 0 °C. DIPEA (190 μL, 0.742 g/mL, 1.09 mmol, 3.6 eq.), HOBt hydrate (55.3 mg, 0.323 mmol, 1.1 eq.), 4,4,4-trifluorobutyric acid (51.2 mg, 0.360 mmol, 1.2 eq.) and EDC·HCl (69.0 mg, 0.360 mmol, 1.2 eq.) were added sequentially in one portion. The ice bath was removed, and the resulting mixture was left stirring overnight at room temperature. The reaction mixture was diluted with EtOAc (50 mL) and quenched with 0.5 M HCl (50 mL). The organic phase was separated, washed with saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$, concentrated under reduced pressure and purified with automated reverse phase liquid chromatography. Gradient elution with H_2O : MeCN = 50 : 50 ⟶ 0 : 100 afforded 4,4,4-trifluoro-1-(6-phenyl-2-azabicyclo[2.2.0]hexan-2-yl)butan-1-one (**iso-377**, 24.5 mg, 0.087 mmol, 29%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.36 – 7.12 (m, 5H), 4.58 (dd, *J* = 17.3, 4.9 Hz, 1H), 4.47 – 4.28 (m, 1H), 4.20 – 4.09 (m, 1H), 3.77 – 3.64 (m, 1H), 3.07 – 2.89 (m, 1H), 2.72 – 2.17 (m, 6H).

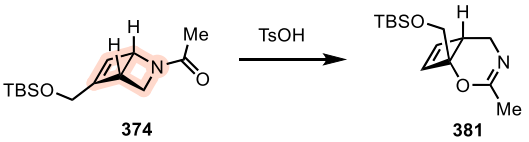
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 169.6, 169.1, 142.8, 142.6, 129.1, 128.7, 127.1, 126.6, 126.5, 126.4, 69.6, 68.6, 58.3, 56.2, 48.1, 46.7, 33.9, 33.2, 29.2 (q, *J* = 29. 4 Hz), 29.1 (q, *J* = 29. 6 Hz), 29.0, 28.8, 28.77, 28.5, 28.3, 24.4 (q, *J* = 2.9 Hz), 24.3 (q, *J* = 2.9 Hz).

R_f = 0.54 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2944 (w), 2878 (w), 1651 (s), 1444 (s), 1383 (m), 1251 (w), 1135 (m), 1105 (m), 978 (w), 753 (w), 700 (w).

HRMS (ESI-TOF) calculated for $C_{15}H_{16}NOF_3+H^+$: 284.1262, found: 284.1264.

Synthesis of 1-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methyl-2-oxa-4-azabicyclo[4.2.0]octa-3,7-diene (**381**)



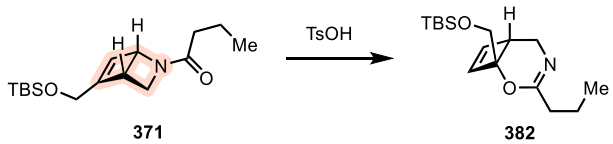
374 **381**

A 4 mL vial was charged with 1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-en-2-yl)ethan-1-one (**374**, 42.8 mg, 0.16 mmol, 1.0 eq.) and MeOH (1.6 mL, 0.1 M). *p*-toluenesulfonic acid (24.4 mg, 0.13 mmol, 0.8 eq.) was added in one portion. TLC analysis showed instantaneous consumption of starting material. The reaction mixture was quenched with minimal amount of saturated aqueous $NaHCO_3$, and solvent was removed under vacuum. The residue was taken up in DCM and filtered through cotton wool. Solvent evaporation afforded 1-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-methyl-2-oxa-4-azabicyclo[4.2.0]octa-3,7-diene (**381**, 40.4 mg, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (d, *J* = 2.8 Hz, 1H), 5.91 (d, *J* = 2.8 Hz, 1H), 3.83 (d, *J* = 11.0 Hz, 1H), 3.72 (d, *J* = 11.1 Hz, 1H), 3.38 (d, *J* = 14.9 Hz, 1H), 3.30 – 3.22 (m, 1H), 3.11 (d, *J* = 5.4 Hz, 1H), 1.92 (d, *J* = 1.8 Hz, 3H), 0.87 (s, 7H), 0.05 (d, *J* = 3.2 Hz, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 141.6, 134.8, 82.2, 66.0, 45.0, 44.7, 25.9, 22.0, -5.1, -5.2.

Synthesis of 1-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-propyl-2-oxa-4-azabicyclo[4.2.0]octa-3,7-diene (**382**)

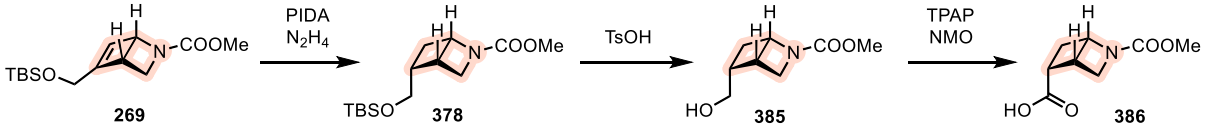


371 **382**

A 4 mL vial was charged with 1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-en-2-yl)butan-1-one (**375**, 51.2 mg, 0.17 mmol, 1.0 eq.) and MeOH (1.7 mL, 0.1 M). *p*-toluenesulfonic acid (25.7 mg, 0.14 mmol, 0.8 eq.) was added in one portion. TLC analysis showed instantaneous consumption of starting material. The reaction mixture was quenched with minimal amount of saturated aqueous $NaHCO_3$, and solvent was removed under vacuum. The residue was taken up in DCM and filtered through cotton wool. Solvent evaporation afforded 1-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-propyl-2-oxa-4-azabicyclo[4.2.0]octa-3,7-diene (**382**, 49.7 mg, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (d, *J* = 2.9 Hz, 1H), 5.89 (d, *J* = 2.9 Hz, 1H), 3.83 (d, *J* = 11.0 Hz, 1H), 3.73 (d, *J* = 11.0 Hz, 1H), 3.41 (d, *J* = 14.9 Hz, 1H), 3.26 (dd, *J* = 14.9, 5.4 Hz, 1H), 3.13 (d, *J* = 5.4 Hz, 1H), 2.21 – 2.05 (m, 2H), 1.65 – 1.50 (m, 2H), 0.89 (m, 12H), 0.04 (d, *J* = 4.2 Hz, 6H).

Synthesis of 2-(methoxycarbonyl)-2-azabicyclo[2.2.0]hexane-5-carboxylic acid (**386**)



To stirred solution of methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**269**, 1.371 g, 4.84 mmol, 1.0 eq.) and hydrazine hydrate (950 μL, 19.4 mmol, 1.021 g/mL, 4.0 eq.) in DCM (5.0 mL) at room temperature was added solution of (diacetoxyiodo)benzene (2.34 g, 7.26 mmol, 1.5 eq.) in DCM (24 mL) over 3 hours using a syringe pump. Afterwards, the reaction mixture was stirred at room temperature until complete, as judged by TLC and LCMS analyses. 50 mL of saturated aqueous $NaHCO_3$ was added and organic phase was separated. The aqueous phase was extracted two more times with 50 mL of DCM. Combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 30 afforded methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**378**, 1.268 g, 4.44 mmol, 92% yield) as a slightly yellow clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.52 (m, 1H), 4.27 (m, 1H), 4.16 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.89 (t, *J* = 9.9 Hz, 1H), 3.75 (dd, *J* = 10.4, 6.1 Hz, 3H), 3.65 (broad s, 3H), 2.98 (m, 1 H), 2.81 (h, *J* = 7.6 Hz, 1H), 2.52 (td, *J* = 12.3, 11.4, 5.3 Hz, 1H), 1.95 (m, 1H), 0.86 (s, 1H), 0.04 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.3, 156.0, 63.1, 60.7, 60.3, 52.2, 51.5, 50.4, 35.6, 35.5, 32.6, 31.7, 31.0, 26.0, 18.4, -5.2, -5.2.

R_f = 0.44 (hexanes : EtOAc = 4 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2954 (s), 2931 (m), 2887 (w), 2857 (w), 1712 (s), 1449 (m), 1381 (s), 1095 (m), 837 (s), 776 (m).

HRMS (ESI-TOF) (ESI-TOF) calculated for $C_{14}H_{27}NO_3Si+Na^+$: 308.1652, found 308.1649.

To a stirred solution of methyl 5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**378**, 0.200 g, 0.701 mmol, 1.0 eq.) in MeOH (7.0 mL, 0.1 M), was added *p*-toluenesulfonic acid monohydrate (0.130 g, 0.624 mmol, 0.9 eq.) in one portion at room temperature. The resulting mixture was stirred for 5 minutes when TLC analysis showed complete consumption of starting material. Excess solid $NaHCO_3$ was added, and solvent was removed under reduced pressure. The crude mixture was directly loaded onto a column. Gradient elution with DCM : MeOH = 100 : 2 ⟶ 100 : 8 afforded methyl 5-(hydroxymethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**385**, 0.117 g, 0.685 mmol, 98%) as a colorless clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.55 (m, 1H), 4.21 (m, 1H), 3.95 (dd, *J* = 10.8, 9.5 Hz, 1H), 3.80 (dd, *J* = 10.8, 6.4 Hz, 1H), 3.65 (s, 3 H), 3.02 (m, 1H), 2.86 (m, 1H), 2.57 (dddd, *J* = 13.5, 11.2, 5.4, 1.0 Hz, 1H), 2.57, 1.97 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.3, 156.0, 62.7, 60.8, 60.4, 52.2, 51.4, 50.4, 35.3, 35.2, 32.3, 31.8, 31.3.

R_f = 0.30 (EtOAc; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3419 (bs), 2958 (m), 2934 (m), 2888 (m), 1685 (bs), 1457 (m), 1391 (m), 1200 (m), 1140 (m).

HRMS (ESI-TOF) calculated for $C_8H_{13}NO_3+H^+$: 172.0968, found 172.0967.

A 20 mL vial was charged with methyl 5-(hydroxymethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**385**, 0.127 g, 0.742 mmol, 1.0 eq.), MeCN (7.0 mL, 0.1 M), NMO hydrate (0.463 g, 3.43 mmol, 4.6 eq.) and TPAP (24.2 mg, 0.069 mmol, 9 mol%). The resulting mixture was stirred for 1 hour at room temperature. Isopropanol was added (2.2 mL) and volatiles were removed under reduced pressure. The residue was redissolved in EtOAc + 1% AcOH (60.6 mL) and passed through a silica plug. The filtrate was concentrated under reduced pressure and excess AcOH was removed azeotropically with toluene to yield 2-(methoxycarbonyl)-2-azabicyclo[2.2.0]hexane-5-carboxylic acid (**386**, 0.133 g, 0.716 mmol, 97%) as a colorless clear oil that solidified on standing in a freezer.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 10.48 (bs, 1H), 4.56 (dm, 1H), 4.27 (m, 2H), 3.68 (s, 3H), 3.64 – 3.54 (m, 1H), 3.39 – 3.19 (m, 1H), 2.73 (td, *J* = 11.4, 9.8, 4.3 Hz, 2H).

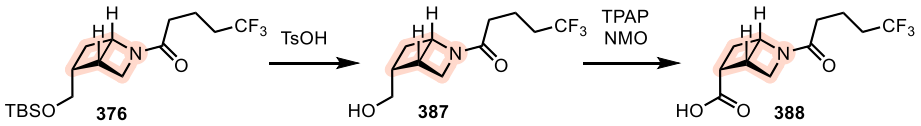
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 178.0, 177.1, 156.4, 156.1, 60.2, 59.7, 53.4, 52.7, 52.6, 52.5, 38.2, 38.1, 33.7, 31.9, 31.5.

R_f = 0.43 (hexanes : EtOAc = 1 : 2 + 1% AcOH; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2959 (w), 2892 (w), 1702 (s), 1678 (s), 1461 (m), 1392 (m), 1197 (m), 852 (w).

HRMS (ESI-TOF) calculated for $C_8H_{11}NO_4+H^+$: 186.0766, found: 186.0767.

Synthesis of 2-(5,5,5-trifluoropentanoyl)-2-azabicyclo[2.2.0]hexane-5-carboxylic acid (**388**)



To a stirred solution of 1-(5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-azabicyclo[2.2.0]hexan-2-yl)-5,5,5-trifluoropentan-1-one (**376**, 45.9 mg, 0.13 mmol, 1.0 eq.) in MeOH (1.3 mL, 0.1 M), was added *p*-toluenesulfonic acid monohydrate (21.4 mg, 0.10 mmol, 0.8 eq.) in one portion at room temperature. The resulting mixture was stirred for 5 minutes when TLC analysis showed complete starting material consumption. Excess solid $NaHCO_3$ was added, and volatiles were removed under reduced pressure. The crude mixture was directly loaded onto a column. Gradient elution with DCM : MeOH = 100 : 3 → 100 : 9 afforded 5,5,5-trifluoro-1-(5-(hydroxymethyl)-2-azabicyclo[2.2.0]hexan-2-yl)pentan-1-one (**387**, 29.0 mg, 0.12 mmol, 92%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 4.64 (m, 1H), 4.44 – 4.13 (m, 2H), 3.98 – 3.78 (m, 2H), 3.13 – 3.01 (m, 1H), 2.91 (m, 1H), 2.65 (m, 1H), 2.23 – 1.81 (m, 7H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 171.3, 170.9, 127.2 (q, *J* = 276.4 Hz), 62.8, 62.5, 60.7, 59.6, 52.1, 49.5, 35.4, 35.1, 33.1 (q, *J* = 28.6 Hz), 32.1, 31.9, 31.7, 31.1, 30.0, 29.8, 17.3 (m).

^{19}F NMR (471 MHz, $CDCl_3$, rotamers) δ -65.89 – -65.99 (m).

R_f = 0.28 (DCM : MeOH = 20 : 1; $KMnO_4$)

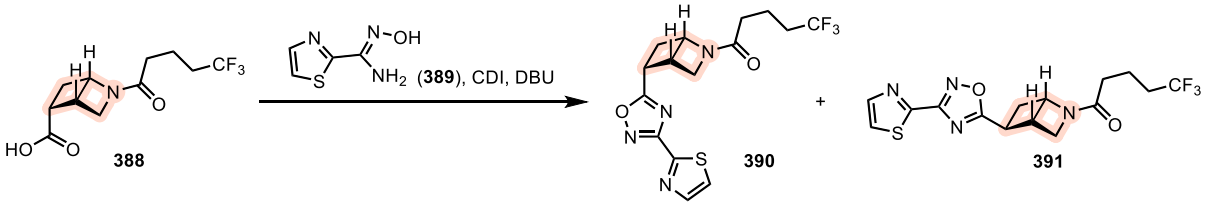
R_f = 0.63 (DCM : MeOH = 10 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 3392 (b), 2938 (w), 2879 (w), 1627 (s), 1678 (s), 1456 (m), 1334 (w), 1249 (m), 1133 (s), 1007 (m).

HRMS (ESI-TOF) calculated for $C_{11}H_{16}NO_2F_3+H^+$: 252.1211, found: 252.1211.

A 4 mL vial was charged with 5,5,5-trifluoro-1-(5-(hydroxymethyl)-2-azabicyclo[2.2.0]hexan-2-yl)pentan-1-one (**387**, 52.7 mg, 0.21 mmol, 1.0 eq.), MeCN (2.5 mL, 0.08 M), NMO hydrate (141.8 mg, 1.05 mmol, 5.0 eq.) and TPAP (7.4 mg, 0.02 mmol, 10 mol%). The resulting mixture was stirred for 1 hour at room temperature. Isopropanol was added (0.75 mL) and solvent was removed under reduced pressure. The residue was redissolved in EtOAc + 1% AcOH and passed through a silica plug (110 mL total). The filtrate was concentrated under reduced pressure and excess AcOH was removed azeotropically with benzene to yield of 2-(5,5,5-trifluoropentanoyl)-2-azabicyclo[2.2.0]hexane-5-carboxylic acid (**388**, 45.5 mg, 0.16 mmol, 82%) as a colorless clear oil, which was used in the next step without further purification.

Synthesis of 5,5,5-trifluoro-1-(5-(3-(thiazol-2-yl)-1,2,4-oxadiazol-5-yl)-2-azabicyclo[2.2.0]hexan-2-yl)pentan-1-one diastereoisomers **390** and **391**



A 4 mL vial was charged with 2-(5,5,5-trifluoropentanoyl)-2-azabicyclo[2.2.0]hexane-5-carboxylic acid (**388**, 38.0mg, 0.14 mmol, 1.0 eq.), MeCN (0.7 mL, 0.2 M) and CDI (27.8 mg, 0.17 mmol, 1.2 eq.). The resulting mixture was stirred for 30 min at room temperature. *N*'-hydroxythiazole-2-carboximidamide[112] (**389**, 24.6 mg, 0.17 mmol, 1.2 eq.) and DBU (40 μL, 0.53 mmol, 1.010 g/mL, 1.9 eq.) were added in one portion and the resulting mixture was heated at 70 °C overnight. Solvent was removed under reduced pressure and residue loaded onto a column. Isocratic elution with EtOAc afforded 5,5,5-trifluoro-1-(5-(3-(thiazol-2-yl)-1,2,4-oxadiazol-5-yl)-2-azabicyclo[2.2.0]hexan-2-yl)pentan-1-one diastereoisomers **390** and **391** in a 1 : 2.3 ratio (31.4 mg, 0.08 mmol, 59%) as colorless clear oils.

Exo isomer (major product, **391**)

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 8.07 (m, 1H), 7.60 (m, 1H), 4.86 (m, 1H), 4.49 (m, 1H), 4.28 (m, 1H), 4.17 – 4.04 (m, 1H), 3.43 (m, 1H), 3.13 (m, 1H), 2.92 (m, 1H), 2.32 – 2.10 (m, 4H), 1.99 – 1.89 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 181.9, 181.8, 171.7, 171.5, 164.3, 164.3, 153.8, 153.7, 145.1, 127.2 (q, *J* = 276.6 Hz), 122.7, 122.7, 61.6, 60.5, 57.9, 55.7, 36.5, 36.4, 36.1, 36.0, 35.4, 34.9, 33.0 (q, *J* = 28.6 Hz), 30.0, 29.8, 17.3 (q, *J* = 3.1 Hz), 17.2 (q, *J* = 3.1 Hz).

^{19}F NMR (471 MHz, $CDCl_3$, rotamers) δ -65.80 – -65.92 (m).

R_f = 0.33 (EtOAc; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3084 (w), 2951 (w), 2881 (w), 1647 (s), 1573 (m), 1453 (s), 1314 (m), 1248 (m), 1133 (m).

HRMS (ESI-TOF) calculated for $C_{15}H_{15}F_3N_4O_2S+Na^+$: 395.0760, found: 395.0756.

Endo isomer (minor product, **390**)

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 8.08 (m, 1H), 7.61 (m, 1H), 4.80 (m, 1H), 4.41 – 4.06 (m, 3H), 3.61 – 3.48 (m, 1H), 3.26 – 3.11 (m, 1H), 3.06 (m, 1H), 2.17 (m, 4H), 1.96 – 1.87 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 180.2, 179.6, 171.1, 170.9, 164.3, 164.3, 127.2 (q, *J* = 276.4 Hz), 60.5, 59.6, 53.1, 5.0, 34.4, 34.1, 33.9, 33.3, 33.1 (q, *J* = 28.6 Hz), 33.1 (q, *J* = 28.5 Hz), 31.7, 31.6, 30.1, 29.8, 17.27 (q, *J* = 3.0 Hz), 17.14 (q, *J* = 3.2 Hz).

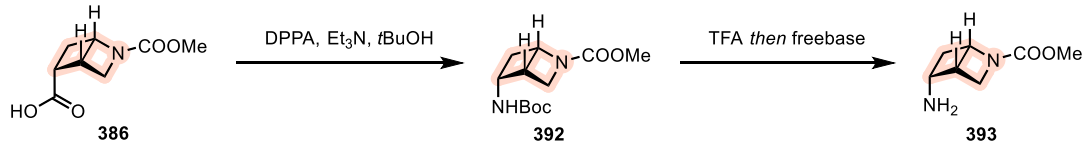
^{19}F NMR (471 MHz, $CDCl_3$, rotamers) δ -65.81 – -65.99 (m).

R_f = 0.18 (EtOAc; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2952 (w), 1645 (s), 1572 (m), 1453 (s), 1312 (m), 1247 (m), 1132 (m), 766 (w).

HRMS (ESI-TOF) calculated for $C_{15}H_{15}F_3N_4O_2S+Na^+$: 395.0760, found: 395.0756.

Synthesis of methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**393**) via Curtius rearrangement



A 20 mL vial was charged with 2-(methoxycarbonyl)-2-azabicyclo[2.2.0]hexane-5-carboxylic acid (**386**, 168.9 mg, 0.91 mmol, 1.0 eq.). The vial was evacuated and refilled with nitrogen 3 times. Anhydrous CCl_4 (4.5 mL, 0.2 M), DPPA (240 μL, 1.280 g/m, 1.12 mmol, 1.2 eq.) and Et_3N (150 μL, 0.726 g/mL, 1.10 mmol, 1.2 eq,) were added sequentially via syringe in one portion. The resulting mixture was refluxed for 1.5 h under nitrogen atmosphere and then cooled to room temperature. *Tert*-butanol (4.5 mL) was added, and the resulting mixture refluxed overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the residue directly loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 75 ⟶ 100 : 100 afforded methyl 5-((*tert*-butoxycarbonyl)amino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**392**, 136.7 mg, 0.53 mmol, 58%) as a colorless clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 5.08 (s, 1H), 4.39 (d, *J* = 35.2 Hz, 2H), 4.17 (d, *J* = 3.9 Hz, 2H), 3.66 (s, 3H), 3.23 (s, 1H), 2.94 (s, 1H), 2.14 – 2.02 (m, 1H), 1.43 (s, 7H).

^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 156.3, 156.0, 155.1, 79.9, 58.8, 58.2, 52.3, 50.0, 49.1, 44.4, 44.2, 37.3, 36.9, 36.2, 28.5.

R_f = 0.39 (hexanes : EtOAc = 2 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 3335 (bs), 2978 (w), 1692 (s), 1516 (m), 1453 (m), 1388 (m), 1171 (m).

HRMS (ESI-TOF) calculated for $C_{12}H_{20}N_2O_4+Na^+$: 279.1321, found: 279.1323.

A 25 mL round bottom flask was charged with 5-((*tert*-butoxycarbonyl)amino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**392**, 136.7 mg, 0.53 mmol, 1.0 eq.) and DCM (4.0 mL, 0.11 M). The resulting solution was cooled to 0 °C in an ice bath and TFA (1.0 m, 1.490 g/mL, 13 mmol, 24 eq.) was slowly added. After 15 minutes, TLC analysis showed full consumption of starting material. Solvent was removed under reduced pressure and the residue directly loaded onto a column. Gradient elution with DCM : MeOH = 100 : 10 ⟶ 100 : 20 (+ 1% concentrated aqueous ammonia) yielded methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**393**, 64.1 mg, 0.41 mmol, 77%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 4.30 (m, 2H), 4.12 (m, 1H), 3.82 (bs, 1H), 3.63 (s, 2H), 3.10 – 3.02 (m, 1H), 2.95 – 2.79 (m, 1H), 1.97 (m, 1H), 1.63 (bs, 2H).

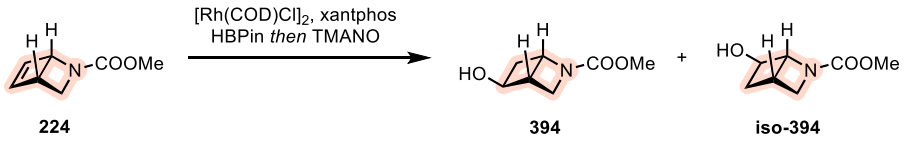
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.3, 155.9, 57.6, 57.2, 52.2, 48.8, 47.9, 46.0, 40.5, 40.2, 37.1, 36.9.

R_f = 0.45 (DCM : MeOH = 10 : 1 + 1% aqueous ammonia; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 3365 (w), 2957 (w), 2886 (w), 1695 (s), 1452 (s), 1382 (s), 1197 (m), 1125 (m), 768 (w).

HRMS (ESI-TOF) calculated for $C_7H_{12}N_2O_2+H^+$: 157.0977, found: 157.0978.

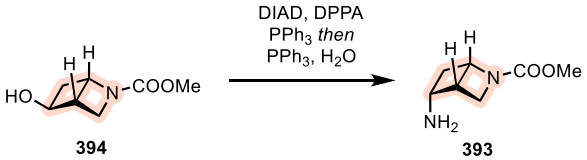
Synthesis of methyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**394**) and methyl 6-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-394**)



224 **394** **iso-394**

A flame dried 4 mL vial was charged with $[Rh(COD)Cl]_2$ (25.4 mg, 0.05 mmol, 1.2 mol%) and xantphos (59 mg, 0.12 mmol, 2.6mol%) in a nitrogen filled glovebox. The vial was taken outside the glovebox and THF (2 mL) was added. The resulting mixture was stirred for 5 minutes at room temperature. Afterwards, methyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**224**, 500 mg, 3.60 mmol, 1.0 eq.) and HBPin (700 μL, 0.882 g/mL, 4.8 mmol, 1.3 eq.) were added sequentially in one portion via syringe. The resulting reaction mixture was stirred at room temperature overnight. ^{1}H NMR analysis of the crude reaction mixture revealed that all starting material was consumed and that the constitutional isomer ratio was 1 : 1.6. Half of the final solution was transferred into a flame dried 50 mL round bottom flask charged with Me_3NO (500 mg, 6.7 mmol, 3.7 eq.) and anhydrous THF (19 mL). The resulting mixture was heated to 65 °C for 1 hour. Volatiles were removed under reduced pressure, and the residue was directly loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 300 ⟶ pure EtOAc afforded methyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**394**) and methyl 6-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-394**) (215.5 mg, 1.4 mmol, 76%) as clear colorless oils.

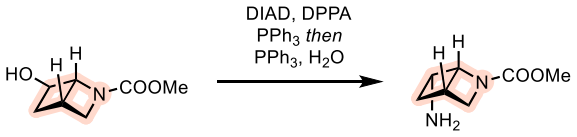
Alternative synthesis of methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**393**) via Mitsunobu inversion and reduction



394 393

A 20 mL vial was charged with methyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**394**, 139.9 mg, 0.890 mmol, 1.0 eq.) and PPh_3 (260.0 mg, 0.991 mmol, 1.1 eq.). The vial was evacuated and refilled with nitrogen 3 times. Anhydrous THF (9 mL, 0.1 M), DIAD (200 μL, 1.040 g/mL, 1.03 mmol, 1.2 eq.) and DPPA (220 μL, 1.227 g/mL, 0.981 mmol, 1.1 eq.) were added sequentially via syringe in one portion. The resulting mixture was left stirring overnight at room temperature. Water (0.9 mL) and PPh_3 (466.9 mg 1.78 mmol, 2.0 eq.) were added, and the resulting mixture was heated to 70 °C for 2 hours. Volatiles were removed under reduced pressure and the residue loaded onto a column. Gradient elution with DCM : MeOH = 10 : 1 ⟶ 10 : 2 (+ 1% aqueous ammonia) afforded methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**393**, 84.3 mg, 0.540 mmol, 61% over 2 steps) as a clear colorless oil. The spectral data matched the product obtained from Curtius rearrangement and deprotection.

Synthesis of methyl 6-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-393**) via Mitsunobu inversion and reduction



iso-394 iso-393

A 20 mL vial was charged with methyl 6-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-394**, 60.6 mg, 0.389 mmol, 1.0 eq.) and PPh_3 (125.4 mg, 0.478 mmol, 1.2 eq.). The vial was evacuated and refilled with nitrogen 3 times. Anhydrous THF (4.5 mL, 0.1 M), DIAD (100 μL, 1.040 g/mL, 0.514 mmol, 1.3 eq.) and DPPA (110 μL, 1.227 g/mL, 0.478 mmol, 1.3 eq.) were added sequentially via syringe in one portion. The resulting mixture was left stirring overnight at room temperature. Water (0.45 mL) and PPh_3 (225.6 mg, 0.860 mmol, 2.2 eq.) were added and the resulting mixture was heated at 70 °C for 2 hours. Volatiles were removed under reduced pressure and the residue loaded onto a column. Gradient elution with DCM : MeOH = 100 : 10 ⟶ 100 : 15 (+ 1% aqueous ammonia) afforded methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-393**, 57.7 mg, 0.369 mmol, 96% over 2 steps) as a clear colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 4.68 (bs, 1H), 4.27 (s, 1H), 3.80 – 3.71 (m, 2H), 3.67 (s, 3H), 2.77 (q, *J* = 10.4 Hz, 1H), 2.49 (s, 1H), 1.92 (s, 3H).

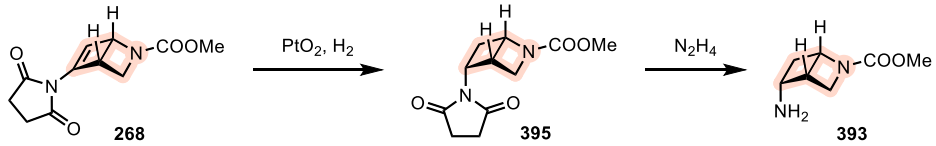
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 157.87, 70.03, 69.56, 59.30, 58.56, 52.44, 50.39, 37.51, 37.15, 24.26, 24.10.

R_f = 0.53 (DCM : MeOH = 10 : 1 + 1% aqueous ammonia; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 3373 (w), 2955 (w), 2879 (w), 1694 (s), 1450 (s), 1382 (s), 1193 (m), 1152 (m), 1128 (m), 768 (w).

HRMS (ESI-TOF) calculated for $C_7H_{12}N_2O_2+H^+$: 157.0977, found: 157.0977.

Alternative synthesis of methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**393**) via reduction and deprotection



268 395 393

A 4 mL vial was charged with methyl 5-(2,5-dioxopyrrolidin-1-yl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**268**, 62.1 mg, 0.263 mmol, 1.0 eq.), EtOAc (5.2 mL, 0.05 M) and PtO_2 hydrate (12.8 mg, 0.052 mmol, 20 mol%). The resulting suspension was purged with hydrogen for 1 minute and left stirring for 1 hour under hydrogen atmosphere (balloon). The suspension was filtered through a PTFE filter to yield, after solvent removal, methyl 5-(2,5-dioxopyrrolidin-1-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**395**, 50.1 mg, 0.210 mmol, 80%) as a colorless clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 4.69 – 4.36 (m, 1H), 4.18 (t, *J* = 8.8 Hz, 1H), 4.06 (m, 1H), 3.67 (m, 3H), 3.47 (m, 2H), 3.22 (m, 1H), 3.08 – 2.93 (m, 1H), 2.70 (s, 4H).

^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 177.6, 177.5, 156.5, 156.0, 58.9, 58.1, 52.4, 51.8, 50.8, 46.4, 46.2, 36.6, 36.0, 33.6, 32.5, 28.5.

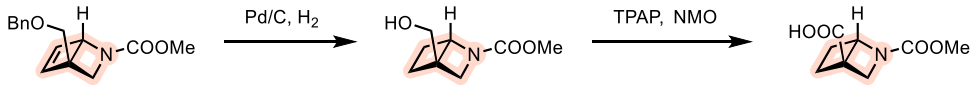
R_f = 0.26 (EtOAc; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2956 (w), 1697 (s), 1450 (m), 1371 (m), 1215 (m), 1128 (m).

HRMS (ESI-TOF) calculated for $C_{11}H_{14}N_2O_4+H^+$: 239.1032, found: 239.1031.

A 4 mL vial was charged with methyl 5-(2,5-dioxopyrrolidin-1-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**395**, 25.7 mg, 0.10 mmol, 1.0 eq.), anhydrous hydrazine (100 μL, 1.021 g/mL, 3.19 mmol, 30 eq.) and MeOH (1 mL, 0.1 M). The resulting solution was heated to 60 °C and left stirring overnight. Volatiles were removed under high vacuum. Crude NMR analysis indicated that reaction was not complete. Deuterated solvent was removed and the residue resubjected to the same reaction conditions except that the temperature was raised to 70 °C. The same workup and purification via flash column chromatography (gradient elution; DCM : MeOH = 100 : 10 ⟶ 100 : 20 + 1% conc. aqueous NH_3) afforded methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**393**, 9.7 mg, 0.062 mmol, 58%) as a colorless film.

Synthesis of 2-(methoxycarbonyl)-2-azabicyclo[2.2.0]hexane-4-carboxylic acid (**397**)



263 396 397

To a stirred solution of methyl 4-((benzyloxy)methyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**263**, 0.437 g, 1.69 mmol, 1.0 eq.) in MeOH (8.5 mL, 0.2 M) was added palladium on carbon (10% w/w, 0.180 g, 10 mol%). The resulting suspension was purged with hydrogen gas for 1 minute and left

stirring under hydrogen atmosphere until TLC showed complete consumption of starting material. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure to afford methyl 4-(hydroxymethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**396**, 0.271 g, 1.59 mmol, 94%) as a colorless clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.45 (d, *J* = 5.0 Hz, 1H), 4.15 (d, *J* = 8.5 Hz, 1H), 4.03 (d, *J* = 8.5 Hz, 1H), 3.69 – 3.65 (m, 5H), 2.42 (m, 1H), 2.26 (m, 3H), 1.77 (bs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.5, 64.1, 63.1, 58.5, 52.3, 43.3, 27.4, 26.3.

R_f = 0.28 (hexanes : EtOAc = 1 : 2; $KMnO_4$)

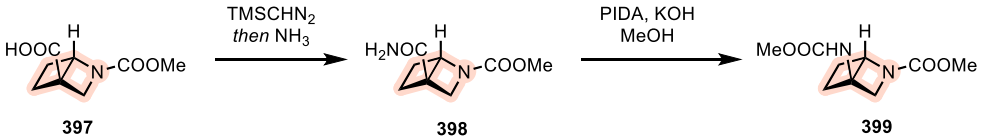
IR (KBr discs, cm^{-1}): 3430 (bs), 2944 (w), 2877 (w), 1685 (s), 1458 (s), 1395 (s), 1199 (w), 1125 (w).

HRMS (ESI-TOF) calculated for $C_8H_{13}NO_3$+Na^+: 194.0788, found: 194.0788.

A 20 mL vial was charged methyl 4-(hydroxymethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**396**, 0.100 g, 0.58 mmol, 1.0 eq.), MeCN (5.5 mL, 0.1 M), NMO hydrate (0.393 g, 3.43 mmol, 4.6 eq.) and TPAP (19.9 mg, 0.06 mmol, 10 mol%). The resulting mixture was stirred for 45 minutes at room temperature. Isopropanol was added (2.0 mL) and volatiles were removed under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 50 → 100 : 125 (+1% AcOH) afforded 2-(methoxycarbonyl)-2-azabicyclo[2.2.0]hexane-4-carboxylic acid (**397**, 0.102 g, 0.55 mmol, 95%) as a colorless clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 11.0 (bs, 1H), 4.71 (m, 1H), 4.55 (m, 1H), 4.15 (m, 1H), 3.68 (s, 3H), 2.87 – 2.75 (m, 1H), 2.59 (m, 1H), 2.42 (m, 1H), 2.28 (m, 1H).

Synthesis of methyl 4-((methoxycarbonyl)amino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**399**)



397 **398** **399**

A 25 mL round bottom flask was charged with 2-(methoxycarbonyl)-2-azabicyclo[2.2.0]hexane-4-carboxylic acid (**397**, 54.0 mg, 0.29 mmol, 1.0 eq.), MeOH (0.7 mL) and benzene (2.1 mL). The resulting solution was cooled to 0 °C in an ice bath. $TMSCHN_2$ solution (0.70 mL 0.6 M in hexanes) was added slowly. The ice bath was removed, and the yellow reaction mixture was left stirring at room temperature for 2 h. Afterwards, neat acetic acid was added dropwise until the reaction mixture became colorless. Volatiles were removed under reduced pressure and the residue loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 20 → 100 : 40 afforded dimethyl 2-azabicyclo[2.2.0]hexane-2,4-dicarboxylate (47.0 mg, 0.24 mmol, 81%) yield as a colorless clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.63 (m, 1H), 4.56 – 4.47 (m, 1H), 4.12 (m, 1H), 3.71 (s, 3H), 3.66 (s, 3H), 2.78 (m, 2H), 2.63 – 2.45 (m, 1H), 2.39 (m, 1H), 2.25 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 171.8, 156.2, 155.9, 66.0, 65.6, 59.2, 58.3, 52.3, 42.9, 27.7, 27.1, 26.7.

A 4 mL vial was charged with dimethyl 2-azabicyclo[2.2.0]hexane-2,4-dicarboxylate (40.3 mg, 0.20 mmol,1.0 eq.) and 2 mL of saturated methanolic ammonia (~ 12 M). The vial was sealed and placed into a preheated heating block at 60 °C for 4 h. After cooling to room temperature, the solvent was removed under reduced pressure to yield methyl 4-((aminooxy)carbonyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**398**, 38.3 mg, 0.19 mmol, 95%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 6.43 – 6.04 (m, 2H), 4.66 (s, 1H), 4.39 (m, 1H), 4.18 (m, 1H), 3.66 (s, 3H), 2.72 – 2.60 (m, 1H), 2.60 – 2.36 (m, 2H), 2.25 (m, 1H).

To a stirred solution of methyl 4-carbamoyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**398**, 9.0 mg, 0.05 mmol, 1.0 eq.) and potassium hydroxide (6.6 mg, 0.12 mmol, 2.4 eq.) in methanol (400 μL, 0.12 M) at 0 °C was added (diacetoxyiodo)benzene (15.6 mg, 0.05 mmol, 1.0 eq.) in one portion. The reaction mixture was brought to room temperature and left stirring overnight. The reaction mixture was partitioned between DCM and water (20 mL each). The organic phase was separated, and the aqueous phase extracted two more times with 20 mL DCM. Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 50 → 100 : 200 afforded methyl 4-((methoxycarbonyl)amino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**399**, 5.7 mg, 0.03 mmol, 54%) as a colorless clear film.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 5.13 (bs, 1H), 4.74 (bs, 1H), 4.22 (bs, 2H), 3.67 (s, 6H), 2.60 – 2.40 (m, 3H), 2.07 (m, 1H).

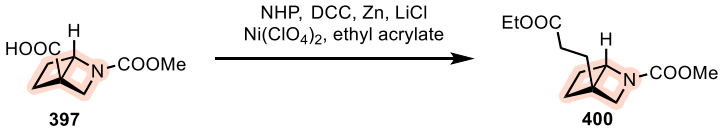
^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.3, 156.0, 155.4, 67.5, 67.0, 62.5, 61.6, 52.5, 52.4, 32.2, 25.0, 24.7.

R_f = 0.49 (hexanes : EtOAc = 1 : 2; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3309 (m), 2953 (w), 1689 (s), 1527 (m), 1457 (m), 1393 (m), 1268 (m).

HRMS (ESI-TOF) calculated for $C_9H_{13}N_2O_4$+Na^+: 237.0846, found: 237.0843.

Synthesis of methyl 4-(3-ethoxy-3-oxopropyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**400**)



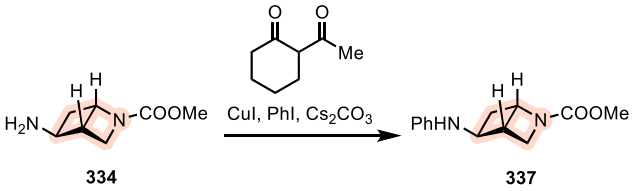
397 **400**

Following the one-pot activation / decarboxylation / Giese addition protocol from the literature[113], a 4 mL vial was charged with 2-(methoxycarbonyl)-2-azabicyclo[2.2.0]hexane-4-carboxylic acid (**397**, 33.0 mg, 0.18 mmol, 1.0 eq.), anhydrous DCM (1 mL), NHPI (32.0 mg, 0.20mmol, 1.1 eq.) and DCC (33 μL, 1.325 g/mL, 0.21 mmol, 1.1 eq.). The resulting mixture was stirred at room temperature until TLC analysis showed full consumption of starting material. All volatiles were removed under high vacuum. Zinc powder (51.4 mg, 0.79 mmol, 4.4 eq.), LiCl (24.4 mg, 0.58 mmol, 3.2 eq.) and $Ni(ClO_4)_2{\cdot}6H_2O$ (36.8 mg, 0.14 mmol, 80 mol%) were added to the residue. The resulting mixture was placed under argon atmosphere and ethyl acrylate (40 μL, 0.940 g/mL, 0.38 mmol, 2.1 eq.) and MeCN (450 μL) were added sequentially in one portion. The resulting suspension was stirred overnight, quenched with water and saturated aqueous NH_4Cl solution, extracted in Et_2O (50 mL). The organic phase was separated,

washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 25 afforded methyl 4-(3-ethoxy-3-oxopropyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**400**, 8.8 mg, 0.04 mmol, 20%) as a colorless film.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.32 (bs, 1H), 4.13 (q, *J* = 7.1 Hz, 1H), 4.03 (d, *J* = 8.6 Hz, 1H), 3.96 (dd, *J* = 8.4, 1.6 Hz, 1H), 3.67 (s, 3H), 2.45 – 2.06 (m, 6H), 1.90 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 2H).

Synthesis of methyl 5-(phenylamino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**337**)



Following the reported procedure[115], a 4 mL vial was charged with methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**334**, 17.7 mg, 0.11 mmol, 1.0 eq.), Cs_2CO_3 (650 mg, 2.0 mmol, 17.6 eq.) and CuI (21.2 mg, 0.11 mmol 1.0 eq.). The vial was evacuated and filled with nitrogen three times. Anhydrous DMF (0.5 mL), iodobenzene (110 μL, 1.830 g/mL, 1.0 mmol. 8.7 eq.), and 2-acetylcyclohexanone (50 μL, 1.078 g/mL, 0.38 mmol, 3.4 eq.) were added sequentially via syringe. The resulting suspension was stirred 3 h at room temperature. Volatiles were removed under high vacuum and the crude mixture loaded directly onto a column. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 60 afforded methyl 5-(phenylamino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**337**, 22.8 mg, 0.10 mmol, 87%) as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.23 – 7.12 (m, 2H), 6.85 – 6.71 (m, 1H), 6.55 – 6.36 (m, 2H), 4.64 (m, 1H), 4.32 (m, 1H), 4.19 – 4.13 (m, 1H), 4.10 (m, 1H), 3.92 (bs, 1H), 3.70 (s, 3H), 3.01 – 2.80 (m, 1H), 2.73 (m, 1H), 2.26 (m, 1H).

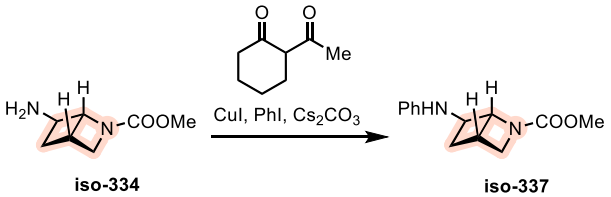
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.5, 146.4, 129.5, 118.3, 113.4, 60.3, 59.8, 55.2, 54.6, 54.6, 54.3, 52.3, 39.1, 38.5, 38.1.

R_f = 0.41 (hexanes : EtOAc = 3 : 2; UV)

IR (ATR-FTIR, cm^{-1}): 3359 (b), 2954 (w), 2877 (w), 1688 (s), 1602 (s), 1503 (m), 1451 (s), 1385 (s), 1198 (m), 1124 (m), 750 (m), 694 (m).

HRMS (ESI-TOF) calculated for $C_{13}H_{16}N_2O_2+H^+$: 233.1290, found: 233.1288.

Synthesis of methyl 6-(phenylamino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-337**)



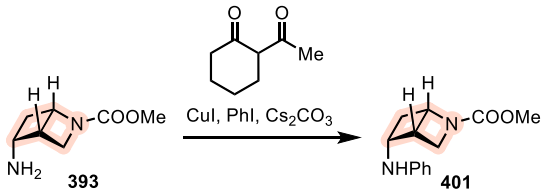
Following the reported procedure[115], a 4 mL vial was charged with methyl 6-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-334**, 43.6 mg, 0.28 mmol, 1.0 eq.), Cs_2CO_3 (650 mg, 2.0 mmol, 7.5 eq.) and CuI (11.2 mg, 0.06 mmol, 19 mol%). The vial was evacuated and filled with nitrogen

three times. Anhydrous DMF (0.5 mL), iodobenzene (110 μL, 1.830 g/mL, 1.0 mmol. 3.5 eq.), and 2-acetylcyclohexanone (29 μL, 1.078 g/mL, 0.22 mmol, 80 mol%) were added sequentially via syringe. The resulting suspension was stirred 3 h at room temperature. Volatiles were removed under high vacuum and the crude mixture loaded directly onto a column. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 60 afforded methyl 6-(phenylamino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-337**, 58.0 mg, 0.25 mmol, 89%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.20 (m, 2H), 6.76 (m, 2H), 6.67 (m, 1H), 4.42 – 4.28 (m, 2H) 4.08 (m, 1H), 3.99 (dm, 1H) 3.85 (bs, 1H), 3.75 (m, 3H), 2.93 (bs, 1H), 2.76 (m, 1H), 2.17 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 156.1, 146.4, 129.4, 129.3, 118.2, 113.6, 113.5, 67.9, 67.0, 57.5, 56.5, 55.7, 55.1, 52.3, 34.9, 34.8, 28.2.

Synthesis of pseudoaxial methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**401**)



Following the reported procedure[115], a 4 mL vial was charged with methyl 5-amino-2-azabicyclo[2.2.0]hexane-2-carboxylate (**393**, 64.1 mg, 0.41 mmol, 1.0 eq.), Cs_2CO_3 (650 mg, 2.0 mmol, 4.9 eq.) and CuI (20.0 mg, 0.11 mmol, 26 mol%). The vial was evacuated and filled with nitrogen three times. Anhydrous DMF (0.5 mL), iodobenzene (110 μL, 1.830 g/mL, 1.0 mmol. 2.4 eq.), and 2-acetylcyclohexanone (64 μL, 1.078 g/mL, 0.49 mmol, 1.2 eq.) were added sequentially via syringe. The resulting suspension was stirred 3 h at room temperature. Volatiles were removed under high vacuum and the crude mixture loaded directly onto a column. Gradient elution with hexanes : EtOAc = 100 : 60 ⟶ 100 : 100 afforded methyl 5-(phenylamino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**401**, 64.3 mg, 0.27 mmol, 67%) as a clear colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 7.17 (m, 2H), 6.72 (m, 1H), 6.50 (m, 2H), 4.49 (m, 1H), 4.25 (m, 1H), 4.18 (m, 2H), 4.10 – 4.02 (m, 1H), 3.68 (s, 3H), 3.28 (bs, 1H), 3.10 – 3.00 (m, 1H), 2.24 – 2.10 (m, 1H).

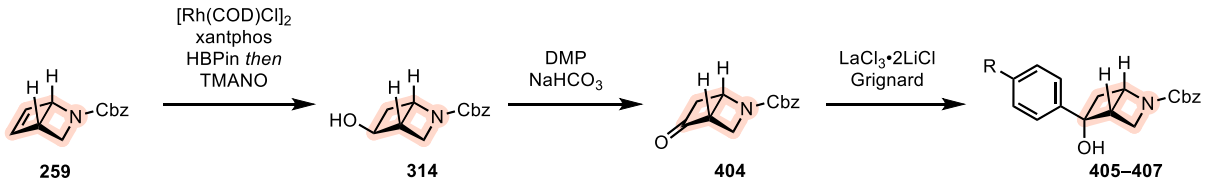
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 156.2, 156.0, 146.9, 146.6, 129.5, 118.1, 112.8, 58.8, 58.5, 52.3, 49.7, 48.8, 47.4, 47.0, 37.5, 37.0, 35.7, 35.6.

R_f = 0.40 (hexanes : EtOAc = 3 : 2; UV)

IR (ATR-FTIR, cm^{-1}): 3362 (b), 2954 (w), 1693 (s), 1603 (m), 1503 (m), 1452 (s), 1387 (s), 1192 (m), 1128 (m), 751 (m).

HRMS (ESI-TOF) calculated for $C_{13}H_{16}N_2O_2+H^+$: 233.1290, found: 233.1286.

Synthesis of benzyl 5-oxo-2-azabicyclo[2.2.0]hexane-2-carboxylate (**404**) and 1,2-Grignard addition products (**405**–**407**)



A flame dried 4 mL vial was charged with $[Rh(COD)Cl]_2$ (25.4 mg, 0.05 mmol, 1.2 mol%) and xantphos (59 mg, 0.12 mmol, 2.6mol%) in a nitrogen filled glovebox. The vial was taken outside the glovebox and THF (2 mL) was added. The resulting mixture was stirred for 5 minutes at room temperature. Afterwards, benzyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**259**, 869 mg, 4.0 mmol, 1.0 eq.) and HBPin (700 μL, 0.882 g/mL, 4.8 mmol, 1.2 eq.) were added in one portion via syringe. The resulting reaction mixture was stirred at room temperature overnight. ^{1}H NMR analysis of the crude reaction mixture revealed that all starting material was consumed and that the product constitutional isomer ratio was 1.7 : 1. The final solution was transferred into a flame dried 100 mL round bottom flask charged with Me_3NO (901 mg, 12.0 mmol, 3.0 eq.) and anhydrous THF (40 mL). The resulting mixture was heated to 65 °C for 1 hour. The solvent was removed under reduced pressure, and the residue was directly loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 200 ⟶ pure EtOAc afforded benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**314**) and benzyl 6-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-314**) (847 mg, 3.6 mmol, 90% over 2 steps) as clear colorless oils. Their spectral data matches the product obtained from uncatalyzed hydroboration / oxidation sequence.

A 20 mL vial was charged benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**314**, 99.5 mg, 0.43 mmol, 1.0 eq.), DCM 4 mL, 0.1 M) and $NaHCO_3$ (71.7 mg, 0.85 mmol, 2.0 eq.). The resulting suspension was cooled to 0 °C in an ice bath and DMP (199.0 mg, 0.47 mmol, 1.1 eq.) was added in one portion. After stirring for 30 minutes at the same temperature, TLC analysis showed full consumption of starting material. The reaction mixture was quenched with 100 μL isopropanol and diluted with 20 mL of 4 : 1 mixture of hexanes and EtOAc. The resulting suspension was stirred for 10 minutes at 0 °C and then filtered through a neutral alumina plug. Evaporation of solvent under reduced pressure furnished benzyl 5-oxo-2-azabicyclo[2.2.0]hexane-2-carboxylate (**404**, 92.2 mg, 0.40 mmol, 94%) as a clear colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.33 (m, 5H), 5.10 (m, 2H), 4.79 (bs, 1H), 4.30 (m, 1H), 4.13 (m 1H), 3.82 (m, 1H), 3.52 – 3.35 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 205.5, 205.1, 155.5, 155.4, 136.3, 128.6, 128.3, 128.1, 67.0, 56.6, 56.3, 56.0, 54.0, 53.4, 50.2, 49.1.

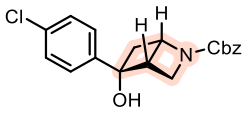
General procedure for 1,2-Grignard addition additive screen

A 4 mL vial was charged with benzyl 5-oxo-2-azabicyclo[2.2.0]hexane-2-carboxylate (**404**, 1.0 eq., normal addition) or 4-chlorophenylmagneisum bromide (1 M, 1.0 eq. or 2.5 eq., inverse order of addition) and anhydrous THF. The resulting solution was cooled to -78 °C and additive ($LaCl_3$·2LiCl or $CeCl_3$) was added. The resulting mixture was stirred for 1 hour at the same temperature before 4-chlorophenylmagnesium bromide (1 M, 1.0 eq. or 2.5 eq, normal order of addition) or THF solution of benzyl 5-oxo-2-azabicyclo[2.2.0]hexane-2-carboxylate (**404**, 1.0 eq., inverse order of addition) was

added. Stirring was continued for 1 h at the same temperature. The reaction mixture was then diluted with Et_2O, quenched with half saturated aqueous ammonium chloride solution, extracted in Et_2O (50 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was redissolved in deuterated chloroform and product yield was determined with ^1H NMR analysis of the crude reaction mixture in the presence of trichloroethylene (1.0 eq.) as an internal standard.

General procedure for oxidation / 1,2-Grignard addition sequence

A 20 mL vial was charged benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**404**, 1.0 eq.), DCM (0.1 M) and $NaHCO_3$ (4.0 eq.). The resulting suspension was cooled to 0 °C in an ice bath and DMP (2.0 eq.) was added in one portion followed by the addition of water (0.9 – 1.4 eq.). The ice bath was removed, and the reaction was left to warm up to room temperature. After TLC analysis indicated full consumption of starting material, the reaction mixture was quenched with isopropanol, diluted with a mixture of hexanes and EtOAc (4 : 1 – 3 : 1), filtered through a plug of neutral alumina and concentrated under reduced pressure. The residue was transferred into a flame dried 50 mL 2 neck round bottom flask and dissolved in anhydrous THF (0.1 M). The resulting solution was cooled to -78 °C and $LaCl_3{\cdot}2LiCl$ (0.6 M solution in THF, 1.0 eq,) was slowly added. The resulting mixture was stirred for 1 h at the same temperature before Grignard reagent solution (1 – 1.5 eq.) was added. Stirring was continued at the same temperature for 1 h before the reaction was quenched with 10% aqueous ammonium chloride and diluted with EtOAc. Saturated Rochelle's salt solution was added and stirring was continued at room temperature until most of the precipitate dissolved. The layers were separated, and the organic phase was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc afforded the desired tertiary alcohol product.

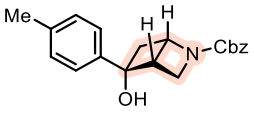
 **405**	Prepared with 4-chlorophenylmagnesium bromide. 90.9 mg, 31% yield over 2 steps on 0.85 mmol scale. Gradient elution with hexanes : EtOAc = 100 : 60 ⟶ 10 : 60. Colorless viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.35 (m, 5H), 5.12 (bs, 2H), 4.68 (m, 2H), 4.49 (bs, 1H), 4.28 (m, 1H), 3.26 (m, 1H), 2.99 (m, 1H), 2.70 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 155.9, 145.6, 136.8, 133.4, 128.9, 128.6, 128.2, 128.1, 126.1, 73.5, 66.8, 55.5, 55.1, 50.5, 49.6, 46.5, 45.9, 42.8, 42.5.

R_f = 0.67 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3400 (bs), 2953 (w), 2878 (w), 1685 (s), 1492 (w), 1423 (m), 1355 (m), 1126 (m), 1012 (w), 833 (w), 735 (w), 697 (w).

 **406**	Prepared with 4-methylphenylmagnesium bromide. 52.5 mg, 43% yield over 2 steps on 0.38 mmol scale. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 80. Colorless viscous oil.

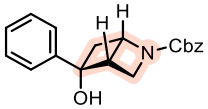
^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.33 m, 6H), 7.19 (m, 2H), 5.13 (m, 2H), 4.71 (bs, 1H), 4.47 – 4.42 (m, 1H), 4.27 (dm, 1H), 3.31 (m, 1H), 3.03 (m, 1H), 2.74 (m, 1H), 2.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 155.9, 155.8, 144.1, 137.3, 136.9, 129.4, 128.6, 128.1, 128.0, 124.6, 73.7, 73.5, 66.7, 55.5, 55.0, 50.5, 49.6, 46.1, 45.5, 42.5, 42.3, 21.1.

R_f = 0.63 (hexanes : EtOAc = 4 : 3; $KMnO_4$)

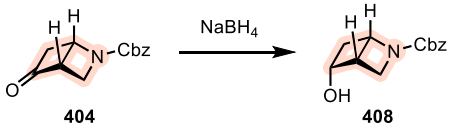
IR (ATR-FTIR, cm^{-1}): 3405 (bs), 2950 (w), 1684 (s), 1421 (s), 1355 (s), 1124 (s), 697 (m).

HRMS (ESI-TOF) calculated for $C_{20}H_{21}NO_3$+Na^+: 346.1419, found: 346.1420.

 **407**	Prepared with phenylmagnesium bromide. 78.4 mg, 53% yield over 2 steps on 0.48 mmol scale. Gradient elution with hexanes : EtOAc = 100 : 60 ⟶ 100 : 80. Colorless viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.51 – 7.25 (m, 9H), 5.14 (bs, 2H), 4.72 (bs, 1H), 4.48 (bs, 1H), 4.29 (bs, 1H), 3.33 (bs, 1H), 3.05 (m, 1H), 2.75 (bs, 1H), 2.59 – 2.30 (m, 1H).

Synthesis of pseudoaxial benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**408**)



404 **408**

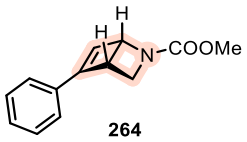
A 4 mL vial was charged with benzyl 5-oxo-2-azabicyclo[2.2.0]hexane-2-carboxylate (**404**, 10.0 mg, 0.04 mmol, 1.0 eq.) and MeOH-d_4 (0.75 mL, 0.06 M). $NaBH_4$ (6.0 mg, 0.2 mmol, 4.0 eq) was added to the resulting solution at 0 °C in two portions. NMR analysis indicated full consumption of starting material and the reaction mixture was quenched with saturated aqueous NH_4Cl, extracted in EtOAc (50 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 50 ⟶ 100 : 150 afforded pseudoaxial benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**408**, 3.2 mg, 0.01 mmol, 32%) as a colorless film.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.40 – 7.29 (bs, 5H), 5.11 (bs, 2H), 4.61 (m, 1H), 4.34 (m, 1H), 4.16 (m, 1H), 3.19 (m, 1H), 2.86 (m, 1H), 2.38 – 2.20 (m, 1H).

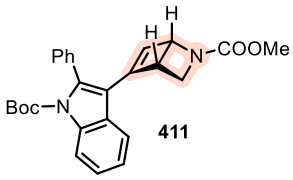
General procedure for Suzuki coupling

A 4 mL vial was charged with vinyl bromide (**265** or **482**, 1.0 eq.), boronic acid pinacol ester (1.2 – 2.0 eq.) and $Pd(PPh_3)_4$ (5 mol%) under nitrogen atmosphere. Anhydrous THF (0.1 – 0.2 M) was added and the resulting solution was warmed up to 45 °C in a heating block. TMSOK (1 M solution in THF, 0.9 eq.) was added and the resulting mixture was stirred for an hour. Afterwards, a second portion of TMSOK (1 M solution in THF, 0.6 eq.; 1.5 eq. in total) was added and the resulting mixture was stirred for an additional hour at the same temperature. The reaction mixture was cooled to room temperature,

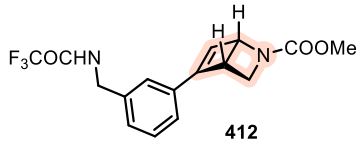
volatiles were removed under reduced pressure, and the residue was purified via flash column chromatography to yield the desired styrene product.

 **264**	Following the general procedure for Suzuki coupling (0.42 mmol scale), **264** was isolated by flash column chromatography (isocratic elution with hexanes : EtOAc = 100 : 100) as a colorless clear oil that solidified on standing in a freezer (77.6 mg, 85% yield).

Spectral data matches the product obtained from dearomatization / 4π-electrocyclization sequence on 4-phenylpyridine.

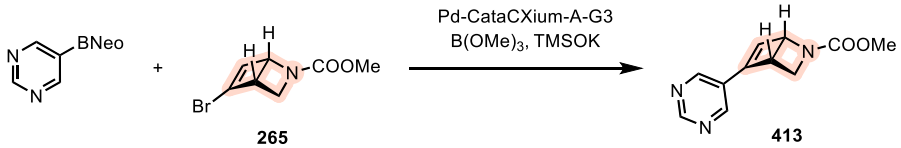
 **411**	Following the general procedure for Suzuki coupling (0.05 mmol scale), **411** was isolated by flash column chromatography (gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 40) as a colorless film (14.1 mg, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 8.30 (m, 1H), 7.74 (bs, 1H), 7.47 – 7.28 (m, 7H), 6.60 (m, 1H), 4.68 (m, 1H), 3.70 – 3.57 (m, 3H), 3.50 – 3.41 (m, 1H), 3.27 (m , 1H), 2.82 (bs, 1H), 1.20 (s, 9H).

 **412**	Following the general procedure for Suzuki coupling (0.05 mmol scale), **412** was isolated by flash column chromatography (gradient elution with hexanes : EtOAc = 100 : 50 ⟶ 100 : 100) as a colorless film (13.2 mg, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.46 – 7.24 (m, 4H), 6.75 (m, 2H), 4.88 (m, 1H), 4.56 (m, 2H), 4.12 (bs, 1H), 3.76 – 3.63 (m, 4H), 3.55 (m, 1H).

Synthesis of methyl 5-(pyrimidin-5-yl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**413**)



Following the reported procedure[121], a 4 ml vial was charged with methyl 5-bromo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**265**, 21.8 mg, 0.100 mmol, 1.0 eq.), Pd-CataCXium A-G3 (2.5 mg, 0.003 mmol, 3 mol%) and freshly resublimed 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)pyrimidine (21.1 mg, 0.110 mmol, 1.1 eq.). The vial was evacuated and refilled with argon 3 times. Anhydrous DME (350 μL, 0.29 M) and $B(OMe)_3$ (34 μL, 0.932 g/mL, 0.300 mmol, 3.0 eq.) were added via syringe in one portion. The resulting mixture was warmed up to 85 °C in a heating block. TMSOK solution in DME (1.0 M, 120 μL, 0.120 mmol, 1.2 eq.) was added and the resulting mixture stirred for

1 hour at 80 °C. After cooling to room temperature, volatiles were removed under reduced pressure and the remaining residue was directly loaded onto a column. Isocratic elution with EtOAc + 1% Et_3N methyl 5-(pyrimidin-5-yl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**413**, 13.5 mg, 0.062 mmol, 62%) as a colorless film.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 9.16 (s, 1H), 8.75 (s, 2H), 6.94 (m, 1H), 4.95 (m, 1H), 4.13 (t, *J* = 7.5 Hz, 2H), 3.79 (ddd, *J* = 7.1, 5.4, 2.7 Hz, 1H), 3.69 (bs, 3H), 3.58 (d, *J* = 8.8 Hz, 1H).

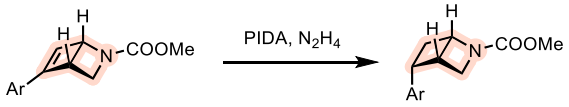
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 158.5, 157.6, 153.6, 146.7, 135.0, 134.5, 126.4, 62.5, 619, 52.5, 49.8, 49.0, 36.7.

R_f = 0.30 (EtOAc + 1% Et_3N; $KMnO_4$)

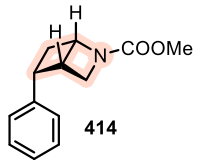
IR (ATR-FTIR, cm^{-1}): 2955 (w), 1706 (s), 1550 (w), 1448 (m), 1407 (w), 1367(s), 1196 (m), 1157 (m), 974 (w).

HRMS (ESI-TOF) calculated for $C_{11}H_{11}N_3O_2$+H^+: 218.0930, found: 218.0928.

General procedure for diimide reduction



Following the reported procedure[144], a 4 mL vial was charged with substrate (1.0 eq.), DCM (1 M) and hydrazine hydrate (4.0 eq.). PIDA (1.5 eq., 0.3 M in DCM) was added dropwise over 3 hours using a syringe pump. Afterwards, the reaction mixture was left stirring overnight, quenched with saturated aqueous $NaHCO_3$ and extracted in DCM (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Flash column chromatography afforded the desired reduced product.



414

Following the general procedure for diimide reduction (0.07 mmol scale), **414** was isolated by flash column chromatography (isocratic elution with hexanes : Et_2O = 100 : 50) as a colorless film (14.8 mg, 96% yield).

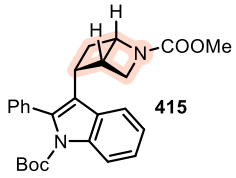
^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 7.35 (m, 2H), 7.26 (bs, 1H), 7.16 (m, 2H), 4.64 (m, 1H), 4.06 (t, *J* = 8.3 Hz, 1H), 3.88 (dd, *J* = 30.4, 8.1 Hz, 1H), 3.66 (m, 2H), 3.34 (bs, 1H), 2.94 (t, *J* = 10.9 Hz, 1H), 2.82 – 2.49 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 156.3, 156.1, 141.0, 140.7, 128.6, 127.4, 126.4, 126.3, 59.9, 59.4, 52.3, 52.2, 51.8, 50.9, 38.6, 38.1, 35.5, 35.4, 33.9, 33.2.

R_f = 0.41 (hexanes : EtOAc = 2 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2954 (w), 2885 (w), 1703 (s), 1448 (m), 1380 (s), 1196 (w), 1127 (m), 757 (w), 700 (w).

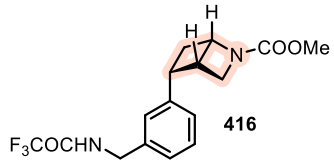
HRMS (ESI-TOF) (ESI-TOF) calculated for $C_{13}H_{15}NO_2$+H^+: 218.1181, found 218.1187.



415

Following the general procedure for diimide reduction (0.03 mmol scale), **415** was isolated by flash column chromatography (gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 50) as a colorless film (12.5 mg, 88% yield).

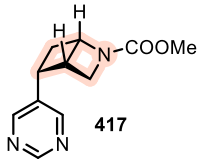
^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 8.29 (m, 1H), 7.56 – 7.23 (m, 8H), 4.46 (m, 1H), 4.14 (m, 1H), 3.93 (m, 1H), 3.77 (m, 1H), 3.62 (m, 2H), 3.13 (n, 1H), 2.90 – 2.72 (m, 1H), 2.46 (dn, 1H), 1.25 (s, 9H).



416

Following the general procedure for diimide reduction (0.04 mmol scale), **416** was isolated by flash column chromatography (gradient elution with hexanes : EtOAc = 100 : 50 ⟶ 100 : 100) as a colorless film (9.6 mg, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.36 (m, 1H), 7.15 (m, 2H), 7.06 (s, 1H), 6.75 (m, 1H), 4.65 (m, 1H), 4.51 (m, 2H), 4.06 (m, 2H), 3.79 (m, 1H), 3.66 (m, 3H), 3.34 (m, 1H), 2.95 (m, 1H), 2.73 – 2.58 (m, 1H).



417

Following the general procedure for diimide reduction (0.05 mmol scale), **417** was isolated by flash column chromatography (gradient elution with DCM : MeOH = 100 : 1 ⟶ 100 : 5) as a colorless film (5.9 mg, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 9.13 (s, 1H), 8.61 (s, 2H), 4.71 (m, 1H), 4.20 – 4.11 (m, 1H), 4.07 (bs, 1H), 3.79 (bs, 1H), 3.67 (bs, 3H), 3.41 (bs, 1H), 3.04 (td, *J* = 13.2, 5.1 Hz, 2H), 2.71 (m, 1H).

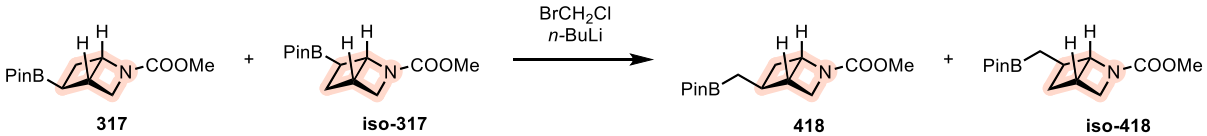
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 157.2, 156.2 (overlapping signals), 133.8, 60.4, 60.0, 52.4, 51.5, 50.7, 35.2, 34.5, 34.3, 33.6, 33.0.

R_f = 0.66 (DCM : MeOH = 10 : 1; UV)

IR (KBr discs, cm^{-1}): 2954 (w), 1702 (s), 1558 (w), 1450 (m), 1412 (w), 1380 (m), 1196 (w), 1129 (w).

HRMS (ESI-TOF) (ESI-TOF) calculated for $C_{11}H_{13}N_3O_2$+H^+: 220.1086, found 220.1084.

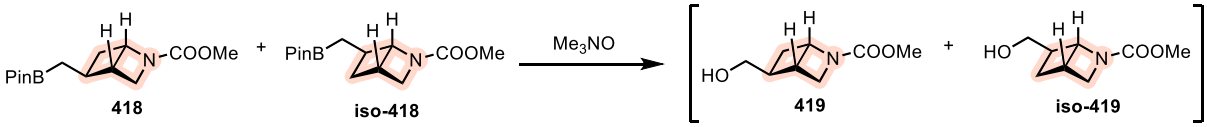
Matteson homologation and oxidation



317 **iso-317** **418** **iso-418**

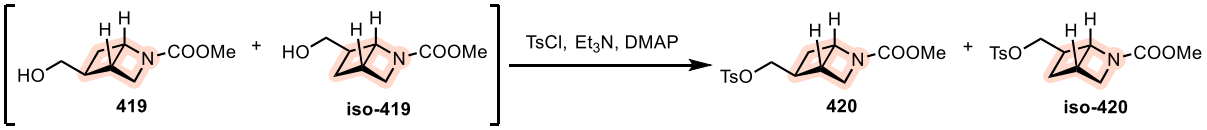
A 50 mL flame dried round bottom flash was charged with a 1.5 : 1 mixture of methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**317**) and methyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-317**) (549 mg, 2.1 mmol, 1.0 eq.) anhydrous THF (20 mL, 0.1 M) and bromochloromethane (340 μL, 1.990 g/mL, 2.5 eq.). The resulting solution was cooled to -78 °C in an acetone/dry ice bath. *n*-BuLi (1.6 M in hexanes, 2.7 mL, 4.3 mmol, 2.1 eq.) was slowly added. After stirring for 5 minutes at the same temperature, dry ice was removed, and the resulting mixture was left to warm up to room temperature. After 26 hours of stirring at room temperature, the reaction mixture was diluted with Et_2O and filtered through a silica plug. Volatiles were removed under reduced pressure to yield a mixture of methyl 5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**418**) and methyl 6-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-418**) (512 mg, 1.8 mmol, 90%) as a slightly yellow oil. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

MS (ESI-Q) calculated for $C_{14}H_{24}BNO_4$+H^+: 282, found: 282.



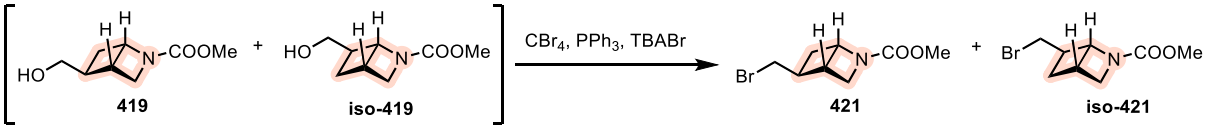
A 50 mL round bottom flask was charged with a mixture of methyl 5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**418**) and methyl 6-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-418**) (512 mg, 1.8 mmol, 1.0 eq.), anhydrous THF (20 mL, 0.1 M) and anhydrous Me_3NO (473 mg, 6.3 mmol, 3.1 eq.) The resulting suspension was heated to 70 °C in a heating block until all starting material was consumed. After cooling to room temperature, volatiles were removed under reduced pressure and the residue loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 400 ⟶ pure EtOAc afforded a mixture of alcohols, which were taken forward to the next step.

Synthesis of methyl 5-((tosyloxy)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**420**) and methyl 6-((tosyloxy)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-420**)



One half of the mixture of alcohols from the previous step was dissolved in DCM (5 mL) and triethylamine (560 μL, 0.726 g/mL, 4.0 mmol), TsCl (763 mg, 4.0 mmol) and DMAP (13. 9 mg, 11 mol%) were added sequentially in one portion. The resulting mixture was stirred overnight. TLC analysis revealed incomplete consumption of starting material. Another portion of DMAP (123 mg, 1 mmol, 1.0 eq.) was added and the resulting mixture was left stirring overnight. Volatiles were removed under reduced pressure and the residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc 100 : 100 ⟶ pure EtOAc afforded a mixture of methyl 5-((tosyloxy)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**420**) and methyl 6-((tosyloxy)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-420**) (138 mg, 0.42 mmol, 42% over 3 steps) as a clear colorless oil. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

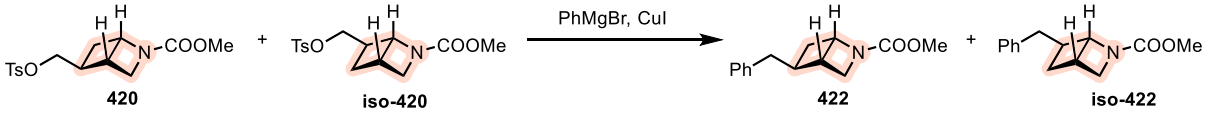
Synthesis of methyl 5-(bromomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**421**) and methyl 6-(bromomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-421**)



A 50 ml round bottom flask was charged with a half of the mixture of alcohols from the oxidation step, PPh_3 (315 mg, 1.2 mmol) and TBABr (32 mg, 0.1 mmol) under nitrogen atmosphere. Anhydrous THF (10 mL) and CBr_4 (398 mg, 1.2 mmol) were added sequentially in one portion. The resulting mixture was left stirring overnight. The reaction mixture was then partitioned between DCM and water. The phases were separated, and the aqueous phase was extracted two more times with DCM. Brine was added to the aqueous phase, which was then extracted 3 more times with EtOAc. Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc 100 : 25 → 100 : 100 afforded a mixture of methyl 5-(bromomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**421**) and methyl 6-(bromomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-421**) (94 mg, 0.4 mmol, 40% over 3 steps) as a clear colorless oil. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

MS (ESI-Q) calculated for $C_8H_{12}BrNO_2$+H^+: 234, found: 234.

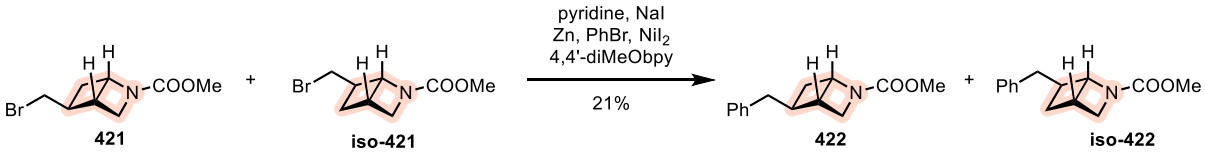
Synthesis of methyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**422**) and methyl 6-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-422**) via substitution



A 4 mL vial was charged with a mixture of methyl 5-((tosyloxy)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**420**) and methyl 6-((tosyloxy)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-420**) (19.2 mg, 0.06 mmol, 1.0 eq.) and CuI (16.4 mg, 0.09 mmol, 1.5 eq.) under nitrogen atmosphere. Anhydrous THF (0.6 mL, 0.1 M) was added, and the resulting suspension was cooled to -78 °C in an acetone/dry ice bath. PhMgBr (3 M in Et_2O, 120 μL, 0.36 mmol, 6.1 eq.) was slowly added. After stirring for 30 minutes at the same temperature, dry ice was removed, and the reaction mixture was slowly brought to room temperature. After 7 hours at room temperature, the reaction was quenched with 10% aqueous NH_4Cl and extracted in Et_2O (50 mL). The organic phase was separated, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc 100 : 25 → 100 : 100 afforded a mixture of methyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**422**) and methyl 6-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-422**) (4.7 mg, 0.02 mmol, 34%) as a colorless film. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

MS (ESI-Q) calculated for $C_{14}H_{17}NO_2$+H^+: 232, found: 232.

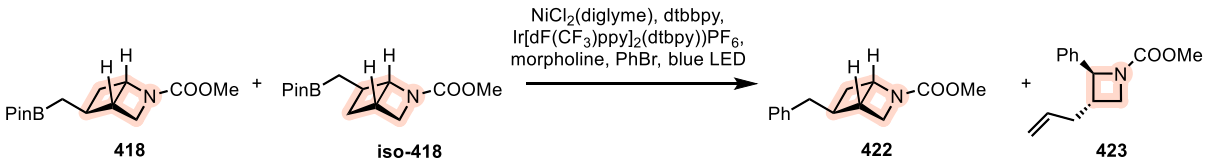
Synthesis of methyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**422**) and methyl 6-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-422**) via cross electrophile coupling



Following the reported procedure[123], a 4 mL vial was charged with a mixture of methyl 5-(bromomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**421**) and methyl 6-(bromomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate **(iso-421**) (23.4 mg, 0.10 mmol, 1.0 eq.), NiI_2, (22.8 mg, 0.07 mmol, 73 mol%), zinc powder (65 mg, 1.0 mmol, 10 eq.), sodium iodide (14.3 mg, 0.10 mmol, 1.0 eq.) and 4,4'-dimethoxy-2,2'-bipyridyl (10.5 mg, 0.05 mmol, 49 mol%) in a nitrogen filled glovebox. The vial was taken outside and anhydrous DMPU (2 mL, 0.05 M), bromobenzene (56 μL, 1.491 g/mL, 0.53 mmol, 5.3 eq.) and pyridine (2 μL, 0.978 g/mL, 0.02 mmol, 20 mol%) were added via syringe. The resulting mixture was stirred for 5 minutes at room temperature and then heated to 60 °C in a metal heating block. When the mixture turned black, it was cooled to room temperature and partitioned between Et_2O (50 mL) and water (50 mL). The organic phase was separated, washed two more times with water, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc 100 : 20 ⟶ 100 : 30 afforded a mixture of methyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**422**) and methyl 6-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-422**) (4.9 mg, 0.02 mmol, 21%) as a colorless film. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

MS (ESI-Q) calculated for $C_{14}H_{17}NO_2$+H^+: 232, found: 232.

Synthesis of methyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**422**) via dual photo/nickel catalyzed cross-coupling



Following the reported procedure[105], a 4 mL vial was charged with $Ni(DME)Cl_2$ (7.4 mg, 0.034 mmol, 5mol%) and dtbbpy (9.4 mg, 0.034 mmol, 5 mol%) in a nitrogen filed glovebox. The vial was taken outside the glovebox and DMF (3.3 mL) was added. The resulting suspension was sonicated for 30 seconds and afterwards heated with a heat gun until a clear green solution was obtained. A second 4 mL vial was charged with $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (7.4 mg, 0.01 mmol, 1 mol%), a mixture of methyl 5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**418**) and methyl 6-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-418**) (188.3 mg, 0.67 mmol, 2.0 eq.), bromobenzene (150 μL, 1.491 g/mL, 2.1 eq.), morpholine (100 μL, 1.030 g/mL, 1.2 mmol, 1.7 eq.) and DMF (3.3 mL). Both solutions were thoroughly mixed, and the resulting mixture was irradiated using blue LEDs for 4.5 hours. Afterwards, it was partitioned between EtOAc (50 mL) and water (50 mL). The organic phase was separated, washed with water two more times, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with hexanes :

EtOAc 100 : 20 ⟶ 100 : 30 afforded methyl 3-allyl-2-phenylazetidine-1-carboxylate (**423**) and methyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**422**, 68.2 mg, 0.30 mmol, 44% based on total mass of starting material) as a clear colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 7.32 – 7.12 (m, 5H), 4.60 (m, 1H), 4.26 (m, 1H), 3.96 (bs, 1H), 3.68 (s, 3H), 2.91 – 2.74 (m, 3H), 2.65 (bs, 1H), 2.54 (m, 1H), 2.16 (bs, 1H).

^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 156.6, 156.3, 139.8, 139.8, 128.6, 128.5, 126.2, 61.1, 60.6, 57.4, 56.5, 52.1, 42.4, 41.3, 41.1, 36.1, 35.7, 35.4.

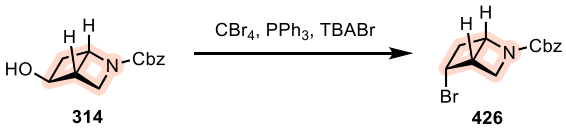
Side product methyl 3-allyl-2-phenylazetidine-1-carboxylate (**423**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 5.72 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.10 – 5.03 (m, 2H), 4.86 (d, *J* = 4.5 Hz, 1H), 4.12 (t, *J* = 8.0 Hz, 1H), 3.69 (dd, *J* = 8.7, 5.5 Hz, 1H), 3.62 (bs, 3H), 2.44 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 141.7, 134.7, 128.8, 127.7, 125.9, 117.3, 69.9, 52.4, 52.2, 39.2, 38.2.

MS (ESI-Q) calculated for $C_{14}H_{17}NO_2$+H^+: 232, found: 232.

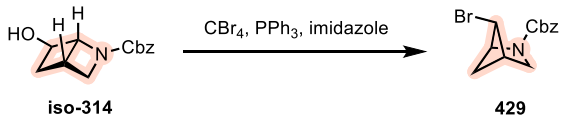
Synthesis of benzyl 5-bromo-2-azabicyclo[2.2.0]hexane-2-carboxylate (**426**)



A 4 ml vial was charged with benzyl 5-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**314**, 46.7 mg, 0.20 mmol), PPh_3 (63.0 mg, 0.24 mmol, 1.2 eq.) and TBABr (6.4 mg, 0.02 mmol, 10 mol%) under nitrogen atmosphere. Anhydrous THF (2 mL, 0.1 M) and CBr_4 (79.6 mg, 0.24 mmol, 1.2 eq.) were added sequentially in one portion. The resulting mixture was left stirring overnight. The reaction solvent was removed under reduced pressure and the residue loaded directly onto a column. Gradient elution with hexanes : EtOAc 100 : 20 ⟶ 100 : 40 afforded benzyl 5-bromo-2-azabicyclo[2.2.0]hexane-2-carboxylate (**426**, 34.4 mg, 0.12 mmol, 58%) as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.35 (m, 5H), 5.21 – 5.08 (m, 2H), 4.89 (m, 1H), 4.68 – 4.52 (m, 2H), 4.33 (qm, 1H), 3.35 – 3.18 (m, 2H), 2.70 (m, 1H).

Synthesis of benzyl 5-bromo-2-azabicyclo[2.1.1]hexane-2-carboxylate (**429**)

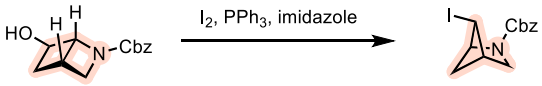


A 4 ml vial was charged with benzyl 6-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-314**, 10.0 mg, 0.04 mmol), PPh_3 (13.5 mg, 0.05 mmol, 1.2 eq.) and imidazole (3.5 mg, 0.05 mmol, 1.2 eq.) under nitrogen atmosphere. Anhydrous toluene (0.4 mL, 0.1 M) and CBr_4 (17.1 mg, 0.05 mmol, 1.2 eq.) were added sequentially in one portion. The resulting mixture was heated to 110 °C for 1 hour. The reaction

solvent was removed under reduced pressure and the residue loaded directly onto a column. Isocratic elution with hexanes : EtOAc 100 : 20 afforded benzyl 5-bromo-2-azabicyclo[2.1.1]hexane-2-carboxylate (**429**, 3.8 mg, 0.01 mmol, 30%) as a clear colorless film. The spectral data matched closely to related compounds.[124]

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.39 – 7.30 (m, 5H), 5.16 (m, 2H), 4.44 (d, *J* = 7.0 Hz, 1H), 3.84 (d, *J* = 8.3 Hz, 1H), 3.57 – 3.48 (m, 2H), 3.08 – 3.00 (m, 1H), 2.98 – 2.90 (m, 1H), 1.66 (t, *J* = 8.3 Hz, 1H).

Synthesis of benzyl 5-iodo-2-azabicyclo[2.1.1]hexane-2-carboxylate (**430**)



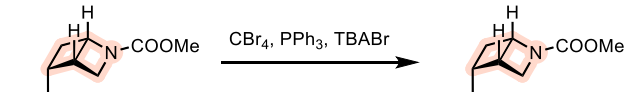
iso-314 **430**

A 10 ml two neck round bottom flask was charged with benzyl 6-hydroxy-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-314**, 60.0 mg, 0.26 mmol), PPh_3 (80.9 mg, 0.31 mmol, 1.2 eq.) and imidazole (21.0 mg, 0.31 mmol, 1.2 eq.) under nitrogen atmosphere. Anhydrous toluene (2.6 mL, 0.1 M) and I_2 (78.3 mg, 0.31 mmol, 1.2 eq.) were added sequentially in one portion. The resulting mixture was heated to 110 °C for 1 hour. Afterwards, it was partitioned between EtOAc (50 mL) and 10% $Na_2S_2O_3$ (50 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc 100 : 3 ⟶ 100 : 50 afforded benzyl 5-bromo-2-azabicyclo[2.1.1]hexane-2-carboxylate (**430**, 29.7 mg, 0.08 mmol, 34%) as a clear colorless oil. The spectral data matched closely to related compounds.[124]

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.40 – 7.29 (m, 5H), 5.16 (n, 2H), 4.46 (d, *J* = 6.1 Hz, 1H), 3.67 (d, *J* = 8.9 Hz, 1H), 3.56 (d, *J* = 8.7 Hz, 1H), 3.46 (d, *J* = 8.7 Hz, 1H), 3.06 – 3.00 (m, 1H), 2.92 (d, *J* = 7.0 Hz, 1H), 1.68 – 1.62 (m, 1H).

^{13}C NMR (101 MHz, C $CDCl_3$, rotamers) δ 155.6, 136.7, 128.7, 128.3, 128.1, 67.2, 65.5, 48.8, 46.6, 40.5, 29.0.

Synthesis of methyl 5-(bromomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**431**)

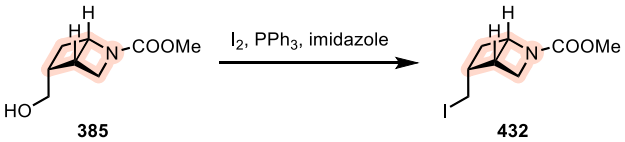


385 **431**

A 4 ml vial was charged with methyl 5-(hydroxymethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**385**, 24.9 mg, 0.14 mmol), PPh_3 (45.6 mg, 0.17 mmol, 1.2 eq.) and TBABr (4.7 mg, 0.02 mmol, 10 mol%) under nitrogen atmosphere. Anhydrous THF (1.4 mL, 0.1 M) and CBr_4 (57.7 mg, 0.17 mmol, 1.2 eq.) were added sequentially in one portion. The resulting mixture was left stirring overnight. The reaction solvent was removed under reduced pressure and the residue loaded directly onto a column. Gradient elution with hexanes : EtOAc 100 : 10 ⟶ 100 : 25 afforded methyl 5-(bromomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**431**, 25.7 mg, 0.11 mmol, 76%) as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 4.52 (m, 1H), 4.26 – 4.15 (m, 2H), 3.63 (m, 5H), 3.10 – 3.01 (m, 2H), 2.67 (m, 1H), 2.01 (m, 1H).

Synthesis of methyl 5-(iodomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**432**)

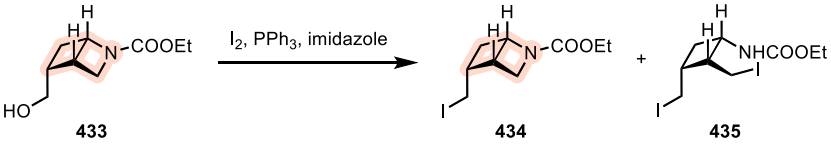


A 4 ml vial was charged with methyl 5-(hydroxymethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**385**, 17.1 mg, 0.10 mmol), PPh_3 (31.5 mg, 0.12 mmol, 1.2 eq.), imidazole (9.2 mg, 0.14 mmol, 1.4 eq.) and anhydrous toluene (1.0 mL, 0.1 M) under nitrogen atmosphere. The resulting solution was cooled to 0 °C in an ice bath and I_2 (30.5 mg, 1.2 mmol, 1.2 eq.) was added in one portion. The ice bath was removed, and the resulting mixture was left stirring overnight. The reaction solvent was removed under reduced pressure and the residue loaded directly onto a column. Gradient elution with hexanes : EtOAc 100 : 10 ⟶ 100 : 30 afforded methyl 5-(iodomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**432**, 24.7 mg, 0.09 mmol, 88%) as a clear colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 4.48 (m, 1H), 4.24 – 4.14 (m, 2H), 3.66 (s, 3H), 3.46 (m, 1H), 3.38 (m, 1H), 3.07 (m, 1H), 2.99 (m, 1H), 2.65 (m, 1H), 1.98 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.2, 155.9, 58.1, 57.6, 52.3, 50.3, 49.4, 36.7, 36.3, 35.9, 34.2, 7.0).

Synthesis of ethyl 5-(iodomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**434**)



A 4 ml vial was charged with ethyl 5-(hydroxymethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**433**, 37.4 mg, 0.20 mmol), PPh_3 (63.0 mg, 0.24 mmol, 1.2 eq.), imidazole (15.8 mg, 0.23 mmol, 1.2 eq.) and anhydrous toluene (2.0 mL, 0.1 M) under nitrogen atmosphere. The resulting solution was cooled to 0 °C in an ice bath and I_2 (66.9 mg, 1.5 mmol, 1.5 eq.) was added in one portion. The ice bath was removed, and the resulting mixture was left stirring overnight. The reaction mixture was partitioned between DCM (20 mL) and 10% aqueous $Na_2S_2O_3$ and brine. The organic phase was separated, and the aqueous phase was extracted two more times with DCM. Combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was loaded onto a column. Gradient elution with hexanes : EtOAc 100 : 15 ⟶ 100 : 20 afforded ethyl 5-(iodomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**434**, 32.3 mg, 0.11 mmol, 54%) and ethyl 2,3-bis(iodomethyl)cyclobutyl)carbamate (**435**; 12.6 mg, 0.03 mmol, 15%) as a clear colorless oils.

Ethyl 5-(iodomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**434**)

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 4.47 (m, 1H), 4.20 – 4.16 (m, 2H), 4.14 – 4.05 (m, 2H), 3.46 (m, 1H), 3.38 (m, 1H), 3.06 (m, 1H), 3.02 – 2.93 (m, 1H), 2.70 – 2.58 (m, 1H), 2.06 – 1.90 (m, 1H), 1.23 (bs, 3H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 155.9, 155.6, 61.0, 58.0, 57.5, 50.2, 49.3, 36.7, 36.2, 35.9, 34.2, 14.9, 7.1.

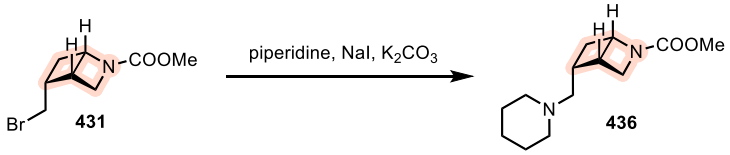
Ethyl 2,3-bis(iodomethyl)cyclobutyl)carbamate (**435**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (bs, 1H), 4.22 – 4.04 (m, 3H), 3.49 (dd, *J* = 9.5, 6.7 Hz, 1H), 3.27 – 3.05 (m, 4H), 2.64 (d, *J* = 7.5 Hz, 1H), 2.54 (ddt, *J* = 12.5, 7.9, 3.9 Hz, 1H), 1.58 (m, 1H), 1.25 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0, 61.3, 46.1, 44.9, 36.7, 35.7, 14.8, 6.4, -1.6.

MS (ESI-Q) calculated for $C_9H_{15}NO_2I_2$+H^+: 424, found: 424.

Synthesis of methyl 5-(piperidin-1-ylmethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**436**) from bromide (**431**)



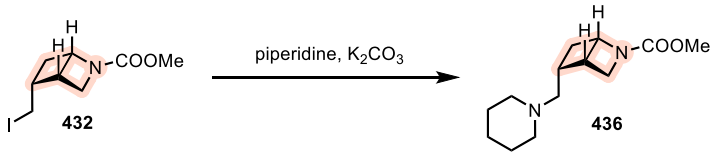
A 4 mL vial was charged with methyl 5-(bromomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**431**, 25.7 mg, 0.11 mmol, 1.0 eq.), MeCN (1.1 mL, 0.1 M), NaI (33.3 mg, 0.22 mmol, 2.0 eq.), K_2CO_3 (60.8 mg, 0.44 mmol, 4.0 eq.) and piperidine (34 μL, 0.862 g/mL, 0.34 mmol, 3.1 eq.) The resulting suspension was heated to 80 °C in a heating block for 1 h when LCMS analysis indicated full consumption of starting material. The reaction mixture was cooled to room temperature, volatiles were removed under reduced pressure and the residue was loaded onto a column. Gradient elution with DCM : MeOH 100 : 2 ⟶ 100 : 8 afforded methyl 5-(piperidin-1-ylmethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**436**, 21.6 mg, 0.09 mmol, 83%) as a slightly yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 4.51 (bs, 1H), 4.28 – 4.16 (m, 2H), 3.64 (s, 3H), 3.61 – 3.43 (m, 1H), 3.35 (m, 1H), 3.24 – 2.92 (m, 6H), 2.85 (m, 1H), 2.03 (s, 5H), 1.67 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 156.2, 60.4, 59.7, 58.7, 53.6, 52.4, 51.3, 50.2, 35.3, 35.0, 33.9, 29.4, 22.9, 22.1.

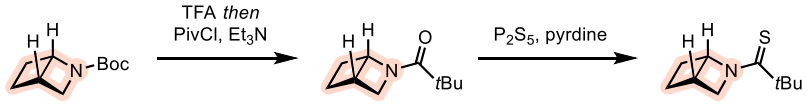
MS (ESI-Q) calculated for $C_{13}H_{22}N_2O_2$+H^+: 239, found: 239.

Synthesis of methyl 5-(piperidin-1-ylmethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**436**) from iodide (**432**)



A 4 mL vial was charged with methyl 5-(iodomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**432**, 22.0 mg, 0.08 mmol, 1.0 eq.), MeCN (0.8 mL, 0.1 M), K_2CO_3 (43.2 mg, 0.31 mmol, 4.0 eq.) and piperidine (24 μL, 0.862 g/mL, 0.24 mmol, 3.1 eq.) The resulting suspension was left stirring at room temperature and 1400 RPM overnight. Volatiles were removed under reduced pressure and the residue loaded onto a column. Gradient elution with DCM : MeOH 100 : 2 ⟶ 100 : 10 afforded methyl 5-(piperidin-1-ylmethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**436**, 10.4 mg, 0.04 mmol, 56%) as a slightly yellow oil. Its spectral data matches the product obtained from bromide (**431**).

Synthesis of 1-(2-azabicyclo[2.2.0]hexan-2-yl)-2,2-dimethylpropane-1-thione (**437**)



362 **438** **437**

A 4 mL vial was charged with *tert*-butyl 2-azabicyclo[2.2.0]hexane-2-carboxylate (**362**, 59.3 mg, 0.324 mmol) and DCM (1.5 mL, 0.2 M). The resulting solution was cooled to 0 °C in an ice bath and purged with argon for 1 minute. TFA (300 μL, 1.490 g/mL, 3.92 mmol, 12 eq.) was added via syringe in one portion. The cooling bath was removed, and the reaction mixture stirred for 15 minutes at room temperature. Volatiles were removed under reduced pressure. Excess TFA was azeotropically removed with MeOH and DCM. Crude residue was redissolved in DCM (1.5 mL) and the resulting solution was cooled to 0 °C In an ice bath. Et_3N (150 μL, 0.726 g/mL, 1.08 mmol, 3.3 eq.) and pivaloyl chloride were added sequentially via syringe in one portion. The cooling bath was removed, and the reaction mixture was left stirring overnight at room temperature. Volatiles were removed and the residue loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 50 ⟶ 100 : 200 afforded 1-(2-azabicyclo[2.2.0]hexan-2-yl)-2,2-dimethylpropan-1-one (**438**, 35.1 mg, 0.210 mmol, 65%) as a colorless clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 4.78 (m, 1H), 4.67 – 3.99 (m, 2H), 2.89 (m, 1H), 2.74 – 2.05 (m, 4H), 1.18 (m, 9H).

^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 178.1, 177.3, 66.4, 63.9, 62.4, 57.4, 38.6, 38.5, 31.2, 31.0, 30.9, 28.8, 27.7, 27.1, 26.4, 25.0.

R_f = 0.50 (hexanes : EtOAc = 1 : 2; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2959 (m), 2875 (w), 1623(s), 1481 (w), 1410 (s), 1363 (w), 1179 (w).

HRMS (ESI-TOF) calculated for $C_{10}H_{17}NO+H^+$: 168.1388, found: 168.1393.

A 4 mL vial was charged with 1-(2-azabicyclo[2.2.0]hexan-2-yl)-2,2-dimethylpropan-1-one (**438**, 28.8 mg, 0.172 mmol, 1.0 eq.), pyridine (600 μL) and P_2S_5 (50.1 mg, 0.225 mmol, 1.3 eq.). The resulting mixture was stirred for 6 hours at 75 °C and then partitioned between aqueous HCl (1 M) and DCM (20 mL). The organic phase was separated, and the aqueous phase extracted two more times with DCM (20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 5 ⟶ 100 : 15 afforded 1-(2-azabicyclo[2.2.0]hexan-2-yl)-2,2-dimethylpropane-1-thione (**437**, 26.6 mg, 0.145 mmol, 84%) as a colorless clear oil.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 5.02 (b, 1H), 4.86 – 4.29 (m, 2H), 2.95 (m, 1H), 2.85 – 2.07 (m, 4H), 1.33 (m, 9H).

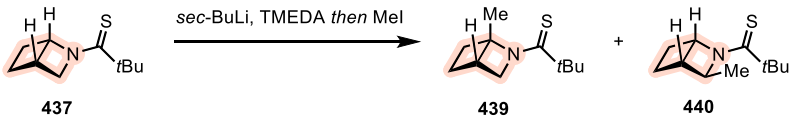
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 209.5, 209.1, 69.7, 69.4, 66.7, 64.1, 43.5, 43.1, 30.5, 30.2, 29.6, 29.6, 29.5, 27.07, 25.9, 24.2.

R_f = 0.51 (hexanes : EtOAc = 5 : 1; UV)

IR (ATR-FTIR, cm^{-1}): 2965 (m), 2939 (m), 2865 (w), 1459 (s), 1446 (s), 1429 (s), 1362 (w), 1253 (m), 1005 (w).

HRMS (ESI-TOF) calculated for $C_{10}H_{17}NS+H^+$: 184.1160, found: 184.1162.

Synthesis of 2,2-dimethyl-1-(1-methyl-2-azabicyclo[2.2.0]hexan-2-yl)propane-1-thione (**439**) and 2,2-dimethyl-1-(3-methyl-2-azabicyclo[2.2.0]hexan-2-yl)propane-1-thione (**440**)



Following the reported procedure[125], 4 mL vial was charged with 1-(2-azabicyclo[2.2.0]hexan-2-yl)-2,2-dimethylpropane-1-thione (**437**, 9.7 mg, 0.05 mmol, 1.0 eq.) and anhydrous THF (300 μL, 0.14 M) under nitrogen atmosphere. The resulting solution was cooled to -78 °C in an acetone/dry ice bath. TMEDA (20 μL, 0.775 g/mL, 0.13 mmol, 2.5 eq.) and *sec*-BuLi (1.3 M in cyclohexane, 0.07 mmol, 1.2 eq.) were added sequentially via syringe. The resulting mixture was stirred for 30 minutes at the same temperature before MeI (10 μL, 2.270 g/mL, 0.16 mmol, 3.0 eq.) was added in one portion. The cooling bath was removed, and the resulting mixture was left stirring for 30 minutes at room temperature before it was quenched with 1 M aqueous HCl. The aqueous phase was extracted with EtOAc (3 x 20 mL). Combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was loaded onto a column. Gradient elution with hexanes : EtOAc 100 : 2 → 100 : 8 afforded a 1 : 1 mixture of 2,2-dimethyl-1-(1-methyl-2-azabicyclo[2.2.0]hexan-2-yl)propane-1-thione (**439**) and 2,2-dimethyl-1-(3-methyl-2-azabicyclo[2.2.0]hexan-2-yl)propane-1-thione (**440**) (3.6 mg, 0.02 mmol, 34% combined yield) as a colorless film.

2,2-dimethyl-1-(1-methyl-2-azabicyclo[2.2.0]hexan-2-yl)propane-1-thione (**439**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (dd, *J* = 10.5, 7.0 Hz, 1H), 4.52 (dd, *J* = 10.5, 1.8 Hz, 1H), 3.04 (ddd, *J* = 14.0, 9.1, 5.6 Hz, 1H), 2.60 (t, *J* = 7.2 Hz, 1H), 2.43 (m, 1H), 2.28 – 2.22 (m, 1H), 2.09 – 1.99 (m, 1H), 1.79 (s, 3H), 1.35 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.2, 79.1, 66.4, 43.5, 34.0, 30.1, 29.5, 23.6, 20.6.

MS (ESI-Q) calculated for $C_{11}H_{19}NS+H^+$: 198, found: 198.

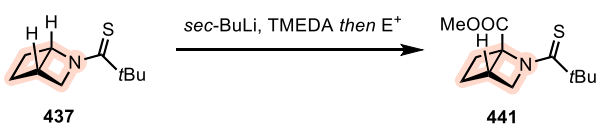
2,2-dimethyl-1-(3-methyl-2-azabicyclo[2.2.0]hexan-2-yl)propane-1-thione (**440**)

^{1}H NMR (500 MHz, $CDCl_3$ δ 5.07 (t, *J* = 5.2 Hz, 1H), 4.98 (qd, *J* = 6.3, 1.8 Hz, 1H), 2.72 (tt, *J* = 13.0, 6.6 Hz, 1H), 2.54 (m, 1H), 2.43 (m, 1H), 2.34 (tt, *J* = 13.1, 6.9 Hz, 1H), 2.22 – 2.16 (m, 1H), 1.56 (d, *J* = 6.4 Hz, 3H), 1.31 (s, 9H).

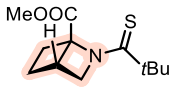
^{13}C NMR (126 MHz, $CDCl_3$) δ 211.0, 72.9, 68.5, 44.4, 36.5, 31.0, 30.8, 23.6, 17.2.

MS (ESI-Q) calculated for $C_{11}H_{19}NS+H^+$: 198, found: 198.

General procedure for directed lithiation / electrophile trapping



A 4 mL vial was charged with 1-(2-azabicyclo[2.2.0]hexan-2-yl)-2,2-dimethylpropane-1-thione (**437**, 18.1 mg, 0.1 mmol, 1.0 eq.) and anhydrous THF (600 μL, 0.14 M) under nitrogen atmosphere. The resulting solution was cooled to the specified temperature. TMEDA (2.7–5.4 eq.) and *sec*-BuLi (1.3 M in cyclohexane, 1.3–2.6 eq.) were added sequentially via syringe. The resulting mixture was stirred for the specified amount of time before the electrophile (3.1–6.1 eq.) was added in one portion. The resulting mixture was left stirring for the specified amount of time at the specified temperature before it was quenched with 10% aqueous NH_4Cl. The aqueous phase was extracted with EtOAc (3 x 20 mL). Combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in deuterated chloroform. Reaction yield was determined by performing ^1H NMR analysis of the crude reaction mixture in the presence of trichloroethylene as an internal standard.



441

Following the general procedure for directed lithiation / electrophile trapping (0.1 mmol scale, Mander's reagent), **441** was isolated by flash column chromatography (gradient elution with hexanes : Et_2O = 100 : 50 ⟶ 100 : 100) as a colorless film (4.3 mg, 18% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.97 – 4.92 (m, 1H), 4.57 (d, *J* = 10.1 Hz, 1H), 3.73 (s, 3H), 3.09 (td, *J* = 12.8, 7.7 Hz, 1H), 2.99 (s, 1H), 2.65 – 2.59 (m, 1H), 2.51 (tt, *J* = 12.1, 6.6 Hz, 1H), 2.10 (q, *J* = 10.8, 10.1 Hz, 1H), 1.38 (s, 9H).

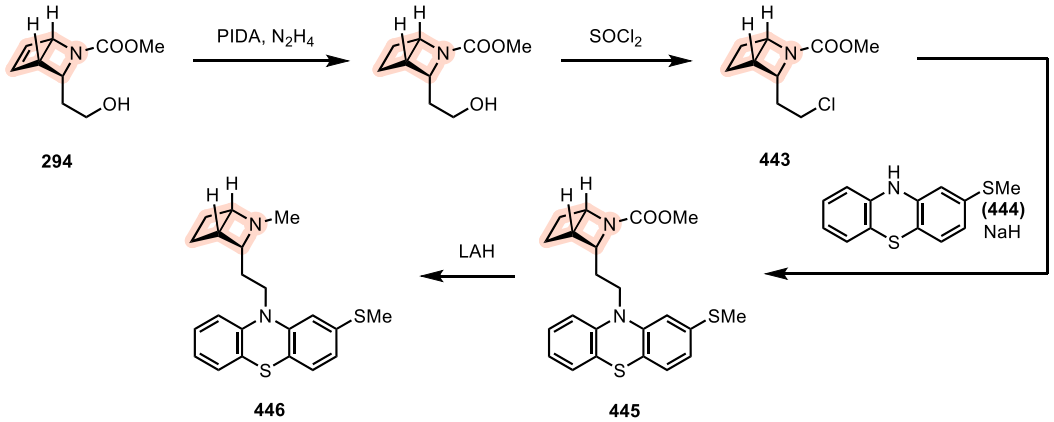
^{13}C NMR (151 MHz, $CDCl_3$) δ 209.8, 168.3, 75.2, 66.1, 52.5, 42.9, 32.8, 29.5, 26.0, 23.9.

R_f = 0.75 (hexanes : EtOAc = 3 : 2; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2950 (m), 1737 (s), 1425 (s), 1395 (w), 1364 (w), 1317 (w), 1252 (w), 1227 (w), 1196 (w), 1181 (w), 1141 (w), 1113 (w).

HRMS (ESI-TOF) calculated for $C_{12}H_{19}NO_2S+H^+$: 252.1215, found: 242.1215.

Synthesis of thioridazine isostere (**446**)



294 **443** **446** **445**

To stirred solution of methyl 3-(2-hydroxyethyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**294**, 0.283 g, 1.54 mmol, 1.0 eq.) and PIDA (0.746 g, 2.32 mmol, 1.5 eq.) in DCM (7.7 mL, 0.2 M) at room temperature was added hydrazine hydrate (450 μL, 9.18 mmol, 1.021 g/mL, 6.0 eq.) in one portion. The reaction mixture was stirred at room temperature overnight. 50 mL of saturated aqueous $NaHCO_3$ was added and organic phase was separated. The aqueous phase was extracted two more times with

20 mL of DCM. Combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 50 ⟶ 100 : 150 afforded methyl 3-(2-hydroxyethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (0.241 g, 1.30 mmol, 84% yield) as a slightly yellow clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.61 (ddd, *J* = 8.8, 7.5, 4.4 Hz, 1H), 4.50 (t, *J* = 5.2 Hz, 1H), 3.77 – 3.70 (m, 2H), 3.65 (s, 3H), 3.04 – 2.97 (m, 1H), 2.56 – 2.44 (m, 1H), 2.41 – 2.15 (m, 4H), 1.88 (bs, 1H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 158.7, 64.13, 62.59, 60.37, 52.44, 35.61, 34.72, 29.63, 19.21.

R_f = 0.38 (hexanes : EtOAc = 1 : 2; $KMnO_4$)

IR (KBr discs, cm^{-1}): 3434 (bs), 2953 (m), 2878 (w), 1683 (s), 1456 (s), 1384 (s), 1195 (w), 1144 (w), 1100 (w), 1608 (w).

HRMS (ESI-TOF) calculated for $C_9H_{15}NO_3$+Na^+: 208.0944, found: 208.0944.

A 4 mL vial was charged with methyl 3-(2-hydroxyethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (40.0 mg, 0.216 mmol, 1.0 eq.), $CHCl_3$ (2.0 mL, 0.1 M) and thionyl chloride (50 μL, 0.69 mmol, 3.2 eq.). The resulting mixture was heated to 65 °C for 30 min in a heating block. Afterwards, the reaction mixture was concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 5 ⟶ 100 : 15 afforded methyl 3-(2-chloroethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**443**, 28.0 mg, 0.137 mmol, 64%) as a colorless clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 4.59 (q, *J* = 6.9 Hz, 1H), 4.49 (m, 1H), 3.63 (m, 5H), 3.00 (dp, *J* = 7.9, 4.0 Hz, 1H), 2.60 – 2.40 (m, 2H), 2.39 – 2.11 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.0, 63.3, 62.1, 52.0, 41.8, 35.3, 33.0, 29.5, 19.1.

R_f = 0.56 (hexanes : EtOAc = 3 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2987 (w), 2954 (w), 1703 (s), 1449 (m), 1375 (m), 1304 (m), 1194 (w), 1137 (w), 1100 (w).

HRMS (ESI-TOF) calculated for $C_9H_{14}NO_2Cl$+H^+: 204.0786, found: 204.0788

HRMS (ESI-TOF) calculated for $C_9H_{14}NO_2Cl$+Na^+: 226.0605, found: 226.0602

A 4 mL vial was charged with 2-(methylthio)-10H-phenothiazine (**444**, 16.9 mg, 0.069 mmol, 1.0 eq.) and sodium amide (3.3 mg, 0.085 mmol, 1.2 eq.) in an argon filled glovebox. The vial was taken outside the glovebox and anhydrous toluene (0.3 mL) was added. The resulting suspension was stirred at 110 °C for 2 hours under nitrogen atmosphere. Toluene solution (0.3 mL) of methyl 3-(2-chloroethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**443**, 14.0 mg, 0.069 mmol, 1.0 eq.) was added via syringe and the resulting mixture was continued stirring at the same temperature for 3 h. The reaction was cooled to room temperature, quenched with saturated NH_4Cl solution, and extracted with EtOAc (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure, and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 3 ⟶ 100 : 25 afforded methyl 3-(2-(2-(methylthio)-10H-phenothiazin-10-yl)ethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**445**, 24.3 mg, 0.060 mmol, 86%) as a colorless clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.20 – 7.11 (m, 2H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.91 (m, 1H), 6.82 (m, 2H), 4.57 (q, *J* = 6.9 Hz, 1H), 4.45 (t, *J* = 4.8 Hz, 1H), 3.96 (m, 2H), 3.60 (s, 3H), 3.01 (tt, *J* = 7.7, 4.5 Hz, 1H), 2.58 – 2.34 (m, 6H), 2.17 – 2.01 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 157.2, 145.8, 145.1, 137.7, 127.7, 127.6, 127.4, 125.63, 122.8, 121.0, 115.9, 114.7, 64.3, 62.3, 52.0, 44.5, 35.7, 29.5, 27.5, 19.2, 16.5.

R_f = 0.75 (hexanes : EtOAc = 1 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2982 (w), 2950 (w), 2864 (w), 1698 (s), 1566 (w), 1455 (s), 1376 (m), 1143 (m), 1112 (m), 802 (w), 732 (w).

HRMS (ESI-TOF) calculated for $C_{22}H_{24}N_2O_2S_2$+Na^+: 435.1171, found: 435.1171.

A 4 mL vial was charged with methyl (2-(2-(methylthio)-10H-phenothiazin-10-yl)ethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**445**, 59.2 mg, 0.143 mmol, 1.0 eq.). The vial was evacuated and refilled with nitrogen 3 times. Anhydrous THF (1.4 mL, 0.1 M) was added, and the resulting solution was cooled to 0 °C in an ice bath. LAH solution in THF (250 μL, 2.4 M in THF, 4.2 eq.) was added and the resulting mixture was stirred at 70 °C for 3 h. Excess LAH was quenched at 0 °C with saturated Rochelle's salt solution. The aqueous phase was extracted with Et_2O and EtOAc (20 mL each). Combined organic phases were washed with brine, dried over $MgSO_4$, concentrated under reduced pressure, and loaded onto a column. Gradient elution with DCM : MeOH = 100 : 2 ⟶ 100 : 10 afforded 10-(2-(2-methyl-2-azabicyclo[2.2.0]hexan-3-yl)ethyl)-2-(methylthio)-10H-phenothiazine (**446**, 30.0 mg, 0.081 mmol, 58%) as a colorless clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 – 7.11 (m, 2H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.91 (t, *J* = 8.3 Hz, 1H), 6.85 – 6.78 (m, 2H), 4.08 – 3.90 (m, 1H), 3.70 (m, 1H), 3.55 (bs, 1H), 3.02 – 2.95 (m, 1H), 2.45 (s, 3H), 2.43 – 2.29 (m, 8H), 2.08 – 1.97 (m, 1H).

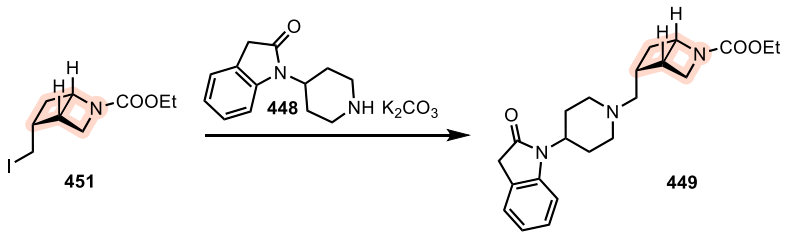
^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6, 144.9, 138.0, 127.7, 127.6, 127.6, 125.7, 123.0, 122.5, 121.1, 116.1, 114.7, 69.8, 68.1, 43.8, 43.6, 34.8, 29.0, 26.9, 19.9, 16.5.

R_f = 0.59 (DCM : MeOH = 10 : 1; $KMnO_4$)

IR (KBr discs, cm^{-1}): 2924 (m), 2850 (w), 2749 (w), 1566 (m), 1458 (s), 1404 (w), 1250 (m), 750 (m), 731 (m).

HRMS (ESI-TOF) calculated for $C_{21}H_{24}N_2S_2$+H^+: 369.1454, found: 369.1451.

Synthesis of muscarinic acetylcholine receptor agonist isostere (**449**)



A 4 mL vial was charged with ethyl 5-(iodomethyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**451**, 37.4 mg, 0.13 mmol, 1.2 eq.), MeCN (1.1 mL, 0.1 M), K_2CO_3 (60.8 mg, 0.44 mmol, 4.1 eq.) and 1-(piperidin-4-yl)indolin-2-one[145] (**448**, 23.0 mg, 0.11 mmol, 1.0 eq.). The resulting suspension was heated to 80 °C in a heating block overnight. After cooling to room temperature, the reaction solvent was removed under reduced pressure and the residue loaded onto a column. Gradient elution with DCM : MeOH 100 : 2 ⟶ 100 : 6 afforded ethyl 5-((4-(2-oxoindolin-1-yl)piperidin-1-yl)methyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**449**, 13.9 mg, 0.04 mmol, 34%) as a slightly yellow film.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.23 (m, 2H), 7.12 (m, 1H), 7.01 (m, 1H), 4.53 (m, 1H), 4.28 (m, 2H), 4.21 (m, 1H), 4.12 (m, 2H), 3.50 (s, 2H), 3.06 – 2.80 (m, 5H), 2.69 (m, 1H), 2.57 (m, 1H), 2.48 – 2.36 (m, 2H), 2.21 – 1.78 (m, 3H), 1.70 – 1.64 (m, 2H), 1.25 (m, 3H).

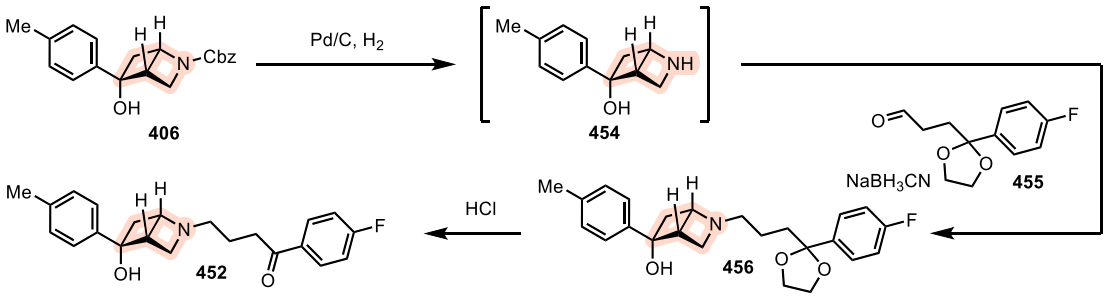
^{13}C NMR (126 MHz, $CDCl_3$, rotamers) δ 175.0, 156.1, 155.7, 143.9, 127.7, 125.0, 124.7, 122.0, 110.4, 60.9, 60.7, 60.2, 59.4, 53.9, 53.0, 51.4, 50.4, 50.0, 36.0, 34.6, 34.3, 33.6, 31.7, 31.6, 28.2, 28.1, 15.0.

R_f = 0.66 (DCM : MeOH = 10 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 2930 (m), 1703 (s), 1612 (w), 1484 (w), 1466 (s), 1346 (m), 1233 (w), 1121 (w), 750 (w).

MS (ESI-Q) calculated for $C_{22}H_{29}N_3O_2$+H^+: 384, found: 384.

Synthesis of Moperone isostere (**452**)



A 4 mL vial was charged with benzyl 5-hydroxy-5-(p-tolyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**406**, 41.7 mg, 0.13 mmol, 1.0 eq.), MeOH (2.5 mL, 0.05 M) and palladium on carbon (13.7 mg, 10% w/w, 0.13 mmol, 10 mol%). The resulting suspension was purged with hydrogen for 2 minutes and left stirring under hydrogen atmosphere (balloon) for 1 hour. The reaction mixture was filtered through a PTFE filter and solvent was removed under reduced pressure. The crude amine **454** was redissolved in MeOH (0.7 mL) and 3-(2-(4-fluorophenyl)-1,3-dioxolan-2-yl)propanal[128] (**455**, 34.7 mg, 0.16 mmol, 1.2 eq.) and $NaBH_3CN$ (24.2 mg, 0.39 mmol, 3.0 eq.) were added sequentially in one portion. The resulting mixture was left stirring for 2 days. The reaction solvent was removed, and the residue was loaded onto a column. Gradient elution with DCM : MeOH 100 : 4 ⟶ 100 : 10 afforded 2-(3-(2-(4-fluorophenyl)-1,3-dioxolan-2-yl)propyl)-5-(p-tolyl)-2-azabicyclo[2.2.0]hexan-5-ol (**456**, 35.6 mg, 0.09 mmol, 70% over 2 steps) as a white foam.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.00 (t, *J* = 8.7 Hz, 2H), 4.81 – 4.73 (m, 1H), 4.34 – 4.27 (m, 1H), 4.22 (t, *J* = 9.7 Hz, 1H), 4.06 – 3.99 (m, 2H), 3.73 – 3.68 (m, 2H), 3.56 (m, 1H), 3.29 (d, *J* = 15.5 Hz, 1H), 3.22 (dt, *J* = 10.3, 6.3 Hz, 2H), 3.05 (ddd, *J* = 15.6, 6.7, 2.4 Hz, 1H), 2.31 (s, 3H), 1.92 (td, *J* = 7.2, 2.3 Hz, 2H), 1.67 (dq, *J* = 15.2, 6.8 Hz, 2H), 0.52 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.7 (d, *J* = 246.4 Hz), 141.9, 137.9, 137.8 (d, *J* = 3.0 Hz), 129.6, 127.6 (d, *J* = 8.2 Hz), 124.6, 115.3 (d, *J* = 21.4 Hz), 109.4, 73.0, 64.7, 60.2, 54.2, 52.5, 42.7, 39.7, 36.7, 21.1, 18.6.

^{19}F NMR (565 MHz, $CDCl_3$) δ -114.0 (tt, *J* = 8.5, 5.4 Hz).

R_f = 0.35 (DCM : MeOH = 20 : 1; $KMnO_4$)

IR (ATR-FTIR, cm^{-1}): 3426 (bs), 2957 (w), 2892 (w), 2335 (s), 2172 (m), 1605 (m), 1507 (s), 1220 (s), 1121 (m), 840 (m), 818 (m).

HRMS (ESI-TOF) calculated for $C_{24}H_{28}NO_3F+H^+$: 398.2131, found: 398.2128.

A 4 mL vial was charged with 2-(3-(2-(4-fluorophenyl)-1,3-dioxolan-2-yl)propyl)-5-(p-tolyl)-2-azabicyclo[2.2.0]hexan-5-ol (**456**, 35.6 mg, 0.09 mmol, 1.0 eq.), THF (1.2 mL) and 1 M HCl (0.6 mL). The resulting mixture was left stirring overnight at room temperature. After LCMS analysis of the crude reaction mixture indicated full consumption of starting material, the reaction mixture was partitioned between 1 M NaOH (50 mL) and DCM : MeOH = 5 : 1 mixture. The organic phase was separated, and the aqueous phase extracted 4 more times with the same mixture of solvents. Combined organic extracts were dried over $MgSO_4$, concentrated under reduced pressure, and loaded onto a column. Isocratic elution with DCM : MeOH 100 : 10 (+ 1% saturated aqueous NH_3) afforded 1-(4-fluorophenyl)-4-(5-hydroxy-5-(*p*-tolyl)-2-azabicyclo[2.2.0]hexan-2-yl)butan-1-one (**452**, 19.2 mg , 0.05 mmol, 61%) as a white amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.37 – 7.28 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 8.6 Hz, 2H), 3.82 (dd, *J* = 8.4, 3.4 Hz, 1H), 3.75 (td, *J* = 5.0, 2.2 Hz, 1H), 3.58 (dd, *J* = 8.4, 7.1 Hz, 1H), 3.30 – 3.23 (m, 1H), 3.11 (bs, 1H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.82 (dd, *J* = 13.7, 2.2 Hz, 1H), 2.67 – 2.57 (m, 3H), 2.34 (s, 3H), 1.77 (p, *J* = 7.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.5, 165.8 (d, *J* = 254.4 Hz), 144.0, 137.0, 133.6 (d, *J* = 2.9 Hz), 130.8 (d, *J* = 9.2 Hz), 129.3, 124.7, 115.8 (d, *J* = 21.7 Hz), 74.1, 56.8, 53.2, 52.4, 43.6, 39.4, 36.3, 22.0, 21.1.

^{19}F NMR (471 MHz, $CDCl_3$) δ -105.5 (ddd, *J* = 13.8, 8.3, 5.5 Hz).

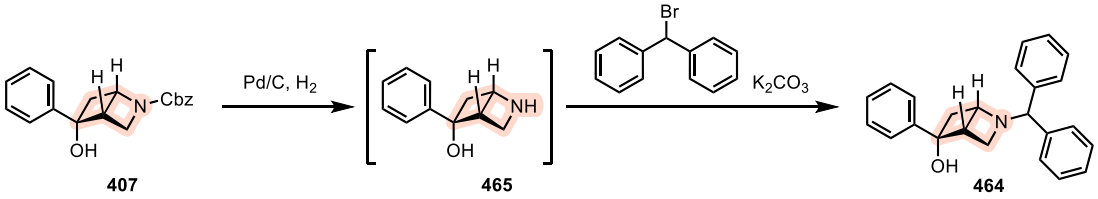
R_f = 0.32 (DCM : MeOH = 20 : 1 + 1% saturated aqueous NH_3; UV)

R_f = 0.69 (DCM : MeOH = 10 : 1 + 1% saturated aqueous NH_3; UV)

IR (ATR-FTIR, cm^{-1}): 3357 (bs), 2939 (m), 1685 (s), 1598 (s), 1506 (m), 1227 (s), 1210 (s), 835 (m), 818 (m).

HRMS (ESI-TOF) calculated for $C_{22}H_{24}NO_2F+H^+$: 354.1896, found: 354.1871.

Synthesis of nociceptin receptor ligand isosteres **464** and **466**



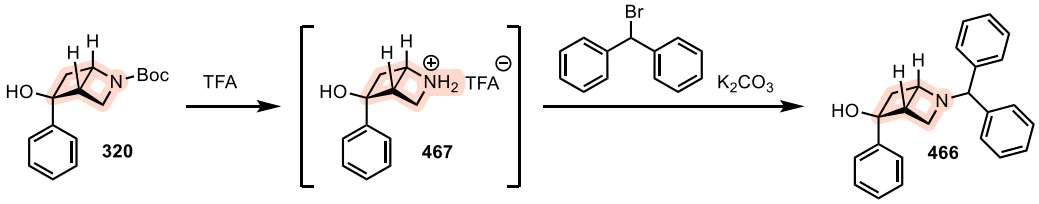
407 **465** **464**

A 4 mL vial was charged with 5-phenyl-2-azabicyclo[2.2.0]hexan-5-ol (**407**, 78.4 mg, 0.25 mmol, 1.0 eq.), MeOH (2.5 mL, 0.1 M) and palladium on carbon (27.0 mg, 10% w/w, 0.03 mmol, 10 mol%). The resulting suspension was purged with hydrogen for 1 minute and left stirring under hydrogen atmosphere (balloon) overnight. The reaction mixture was filtered through a PTFE filter and solvent was removed under reduced pressure. The crude amine **465** was redissolved in DMF (2.5 mL) and freshly recrystallized bromodiphenylmethane (68.0 mg, 0.28 mmol, 1.1 eq.) and K_2CO_3 (38.0 mg, 0.28 mmol, 1.1 eq.) were added sequentially in one portion. The resulting mixture was left stirring for 1.5 h. The reaction solvent was removed under high vacuum and the residue was loaded onto a column. Gradient elution with DCM : MeOH 100 : 2 ⟶ 100 : 3 (+ 1% Et_3N) afforded 2-benzhydryl-5-phenyl-2-azabicyclo[2.2.0]hexan-5-ol (**464**, 26.1 mg, 0.08 mmol, 30% over 2 steps) as orange amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.49 (m, 2H), 7.46 – 7.40 (m, 4H), 7.36 (m, 1H), 7.33 – 7.24 (m, 6H), 7.23 – 7.16 (m, 2H), 4.83 (s, 1H), 3.79 (dd, *J* = 8.7, 3.4 Hz, 1H), 3.75 (m, 1H), 3.57 (t, *J* = 8.0 Hz, 1H), 3.31 – 3.26 (m, 1H), 2.95 – 2.90 (m, 1H), 2.52 (ddd, *J* = 13.7, 5.4, 2.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.8, 142.0, 141.8, 128.7, 128.6, 128.6, 127.9, 127.7, 127.3, 127.3, 124.7, 74.5, 71.9, 56.3, 52.6, 42.8, 40.2.

MS (ESI-Q) calculated for $C_{24}H_{23}NO+H^+$: 342, found: 342.

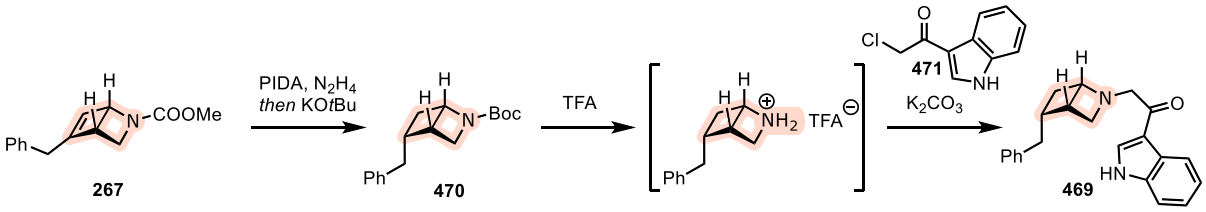


A 4 mL vial was charged with *tert*-butyl 5-hydroxy-5-phenyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**320**, 55.0 mg, 0.20 mmol, 1.0 eq.), DCM (0.8 mL) and TFA (200 μL, 1.490 g/mL, 2.6 mmol, 13.0 eq.) The resulting mixture was left stirring at room temperature for 15 minutes. Solvent was removed under reduced pressure. Excess TFA was azeotropically removed with MeCN. The crude ammonium salt **467** was redissolved in MeCN (2.0 mL). Freshly recrystallized bromodiphenylmethane (59.3 mg, 0.24 mmol, 1.2 eq.) and K_2CO_3 (99.5 mg, 0.72 mmol, 3.6 eq.) were added sequentially in one portion. The resulting mixture was left stirring for 1.5 h. The reaction solvent was removed under high vacuum and the residue was loaded onto a column. Gradient elution with DCM : MeOH 100 : 2 ⟶ 100 : 5 afforded 2-benzhydryl-5-phenyl-2-azabicyclo[2.2.0]hexan-5-ol (**466**, 36.6 mg, 0.11 mmol, 54% over 2 steps) as an orange amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.14 (m, 15H), 4.64 (s, 1H), 4.16 (td, *J* = 5.4, 2.8 Hz, 1H), 3.65 – 3.59 (m, 1H), 3.41 – 3.37 (m, 1H), 3.24 (dt, *J* = 7.9, 4.1 Hz, 1H), 2.87 (dd, *J* = 9.1, 4.7 Hz, 1H), 2.27 (ddd, *J* = 13.9, 5.9, 3.3 Hz, 1H).

MS (ESI-Q) calculated for $C_{24}H_{23}NO+H^+$: 342, found: 342.

Synthesis of GluN2B/NMDAR ligand isosteres **469** and **472**



To stirred solution of methyl 5-benzyl-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**267**, 0.600 g, 2.6 mmol, 1.0 eq.) and hydrazine hydrate (510 μL, 1.021 g/mL, 10.4 mmol, 1.0 eq.) in DCM (2.6 mL, 1.0 M) was added PIDA (1.270 g, 3.9 mmol, 1.5 eq. in 13 mL DCM) dropwise via a syringe pump at room temperature over 3 hours. The reaction mixture was stirred at room temperature overnight. 50 mL of saturated aqueous $NaHCO_3$ was added and organic phase was separated. The aqueous phase was extracted two more times with 20 mL of DCM. Combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. ^{1}H NMR analysis indicated that reduction was not complete. The residue was redissolved in MeOH (13 mL, 0.2 M) and PtO_2 hydrate (29.5 mg, 0.13 mmol, 5 mol%) was added. The resulting suspension was purged with hydrogen for 1 minute and then left stirring under hydrogen atmosphere (balloon). When LCMS analysis showed complete consumption of starting material, the reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The crude product was purified via flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 60 afforded methyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (0.573 g, 2.5 mmol, 95% yield) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.26 (m, 2H), 7.18 (m, 1H), 7.12 (m, 2H), 4.52 (m Hz, 1H), 4.37 (m, 1H), 4.18 (m, 1H), 3.74 – 3.64 (m, 3H), 2.98 (m, 4H), 2.66 (bs, 1H), 2.17 – 1.99 (m, 1H).

MS (ESI-Q) calculated for $C_{14}H_{17}NO_2$+H^+: 232, found: 232.

A 4 mL vial was charged with methyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (92.4 mg, 0.40 mmol, 1.0 eq.) and THF (2.0 mL). The resulting solution was cooled to 0 °C in an ice bath. KO*t*Bu solution (480 μL, 1M in THF, 0.48 mmol, 1.2 eq.) was canulated to the substrate solution. After the addition was complete, the ice bath was removed, and the resulting brown solution was stirred at room temperature overnight. The reaction solvent was removed under reduced pressure and the residue loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 30 afforded *tert*-butyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**470**, 94.2mg, 0.34 mmol, 86%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.30 (m, 2H), 7.21 (m, 1H), 7.15 (m, 2H), 4.48 (m, 1H), 4.41 – 4.29 (m, 1H), 4.14 (m, 1H), 3.00 (bs, 4H), 2.71 – 2.60 (bs, 1H), 2.20 – 2.00 (m, 1H), 1.49 (m, *J* = 14.8 Hz, 9H).

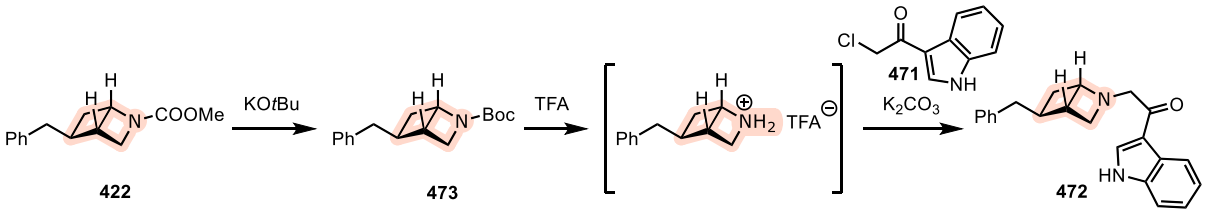
A 4 mL vial was charged with *tert*-butyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**470**, 14.6 mg, 0.05 mmol, 1.0 eq.), DCM (0.4 mL) and TFA (100 μL, 1.490 g/mL, 1.3 mmol, 24 eq.) The resulting mixture was left stirring at room temperature for 15 minutes. Solvent was removed under reduced pressure. Excess TFA was azeotropically removed with MeCN. The crude ammonium salt was redissolved in MeCN (0.5 mL). 2-chloro-1-(1H-indol-3-yl)ethan-1-one[146] (**468**, 10.6 mg, 0.05 mmol, 1.0 eq.) and K_2CO_3 (27.6 mg, 0.20 mmol, 3.7 eq.) were added sequentially in one portion. The resulting

mixture was left stirring for 1 h. The reaction solvent was removed under reduced pressure and the residue was loaded onto a column. Gradient elution with DCM : MeOH 100 : 5 ⟶ 100 : 15 (+ 1% saturated aqueous NH_3) afforded 2-(5-benzyl-2-azabicyclo[2.2.0]hexan-2-yl)-1-(1H-indol-3-yl)ethan-1-one (**471**, 11.2 mg, 0.03 mmol, 64% over 2 steps) as an orange amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.67 (bs, 1H), 8.12 – 8.05 (m, 1H), 7.62 (s, 1H), 7.42 – 7.35 (m, 1H), 7.20 – 7.14 (m, 3H), 7.10 (m, 3H), 7.00 (m, 2H), 4.20 (bs, 1H), 4.11 – 4.03 (m, 1H), 3.93 (m, 1H), 3.86 (s, 2H), 3.00 (bs, 1H), 2.81 (m, 3H), 2.51 (m, 1H), 2.38 – 2.29 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.4, 139.9, 136.6, 133.1, 128.7, 128.5, 126.2, 125.4, 123.8, 122.9, 121.8, 115.1, 112.4, 63.4, 57.8, 55.0, 36.5, 35.6, 35.4, 28.3.

MS (ESI-Q) calculated for $C_{22}H_{22}N_2O+H^+$: 331, found: 331.



KO*t*Bu solution (1.4 mL, 1M in THF, 1.4 mmol, 4.7 eq.) was canulated to methyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**422**, 68.2 mg, 0.30 mmol, 1.0 eq.) at 0 °C. After the addition was complete, the ice bath was removed, and the resulting brown solution was stirred at room temperature overnight. The reaction solvent was removed under reduced pressure and the residue was loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 10 ⟶ 100 : 20 afforded *tert*-butyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**473**, 66.3 mg, 0.24 mmol, 82%) as a colorless clear oil.

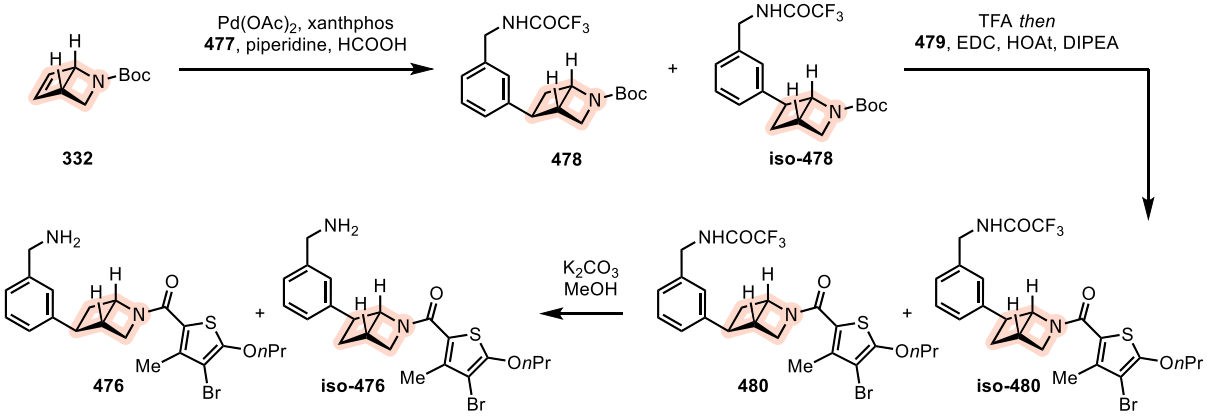
^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.33 – 7.28 (m, 2H), 7.22 (tm, 1H), 7.17 (m, 2H), 4.54 (m, 1H), 4.20 (m, 1H), 4.00 – 3.85 (m, 1H), 2.82 (m, 3H), 2.65 – 2.45 (m, 2H), 2.15 (m, 1H), 1.46 (bs, 9H).

A 4 mL vial was charged with *tert*-butyl 5-benzyl-2-azabicyclo[2.2.0]hexane-2-carboxylate (**473**, 66.3 mg, 0.24 mmol, 1.0 eq.), DCM (1.0 mL) and TFA (250 μL, 1.490 g/mL, 3.3 mmol, 13 eq.) The resulting mixture was left stirring at room temperature for 15 minutes. Solvent was removed under reduced pressure. Excess TFA was azeotropically removed with MeCN. The crude ammonium salt was redissolved in MeCN (2.4 mL). 2-chloro-1-(1H-indol-3-yl)ethan-1-one[146] (**471,** 49.3 mg, 0.26 mmol, 1.0 eq.) and K_2CO_3 (132.3 mg, 0.96 mmol, 4.0 eq.) were added sequentially in one portion. The resulting mixture was left stirring for 4 h. The reaction solvent was removed under reduced pressure and the residue was loaded onto a column. Gradient elution with DCM : MeOH 100 : 5 ⟶ 100 : 10 (+ 1% saturated aqueous NH_3) afforded 2-(5-benzyl-2-azabicyclo[2.2.0]hexan-2-yl)-1-(1H-indol-3-yl)ethan-1-one (**472,** 40.4 mg, 0.12 mmol, 50% over 2 steps) as an orange amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.76 (bs, 1H), 8.37 – 8.33 (m, 1H), 7.90 (s, 1H), 7.44 – 7.40 (m, 1H), 7.33 – 7.15 (m, 7H), 4.30 – 4.24 (m, 1H), 3.99 (dd, *J* = 8.6, 6.9 Hz, 1H), 3.89 (s, 2H), 3.47 (dd, *J* = 8.6, 3.3 Hz, 1H), 2.83 – 2.65 (m, 5H), 1.92 (dt, *J* = 12.5, 5.6 Hz, 1H).

MS (ESI-Q) calculated for $C_{22}H_{22}N_2O+H^+$: 331, found: 331.

Synthesis of β-tryptase inhibitor isosteres **476**, **iso-476** and **481**



A 4 mL vial was charged with *tert*-butyl 2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**332**, 90.5 mg, 0.50 mmol, 1.0 eq.), DMF (2.5 mL, 0.2 M), 2,2,2-trifluoro-*N*-(3-iodobenzyl)acetamide[147] (**477**, 246.8 mg, 0.75 mmol, 1.5 eq.), piperidine (150 μL, 0.862 g/mL, 1.5 mmol, 3.0 eq.), formic acid (40 μL, 1.220 g/mL, 1.1 mmol, 2.1 eq.), $Pd(OAc)_2$ (6.0 mg, 0.03 mmol, 5 mol%) and xantphos (29.0 mg, 0.05 mmol, 10 mol%). The resulting mixture was degassed by sparging with argon for 3 minutes and then heated to 50 °C for 2 h in a heating block. The reaction mixture was cooled to room temperature and the solvent was removed under high vacuum. The residue was loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 80 afforded a mixture of *tert*-butyl 5-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**489**) and *tert*-butyl 6-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-478**) (151.0 mg, 0.39 mmol, 79%) as a slightly yellow clear oil. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

A 4 mL vial was charged with a mixture of *tert*-butyl 5-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**478**) and *tert*-butyl 6-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**iso-478**) (151.0 mg, 0.39 mmol, 79%), DCM (1.6 mL) and TFA (0.4 mL, 1.490 g/mL, 5.2 mmol, 13 eq.). The resulting mixture was stirred for 15 minutes at room temperature. Solvent was removed under reduced pressure. Crude residue was redissolved in DMF (4.0 mL), and the resulting solution was cooled to 0 °C in an ice bath. Thiophene carboxylic acid **479**[148] (113.2 mg, 0.41 mmol, 1.0 eq.), HOAt (67.0 mg, 0.49 mmol, 1.3 eq.), DIPEA (260 μL, 0.742 g/mL, 1.5 mmol, 3.8 eq.) and EDC (94.3 mg, 0.49 mmol, 1.3 eq.) were added sequentially in one portion. The cooling bath was removed, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with EtOAc (50 mL), washed with 1 M aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL) and then dried over $MgSO_4$. Solvent was removed under reduced pressure to yield a crude mixture of amides **480** and **iso-480**, which was used in the next step without further purification.

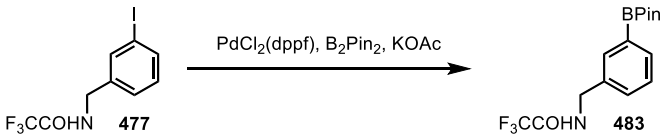
MS (ESI-Q) calculated for $C_{23}H_{24}BrF_3N_2O_3S+H^+$: 545, found: 545.

A 25 mL round bottom flask was charged with a crude mixture of amides **480** and **iso-480**, MeOH (3.5 mL) and water (0.7 mL). K_2CO_3 (283.3 mg) was added to the resulting mixture in one portion. After stirring for 8 h at room temperature, volatiles were removed under reduced pressure and the residue was directly loaded onto a column. Gradient elution with DCM : MeOH = 100 : 10 ⟶ 100 : 40 (+ 1%

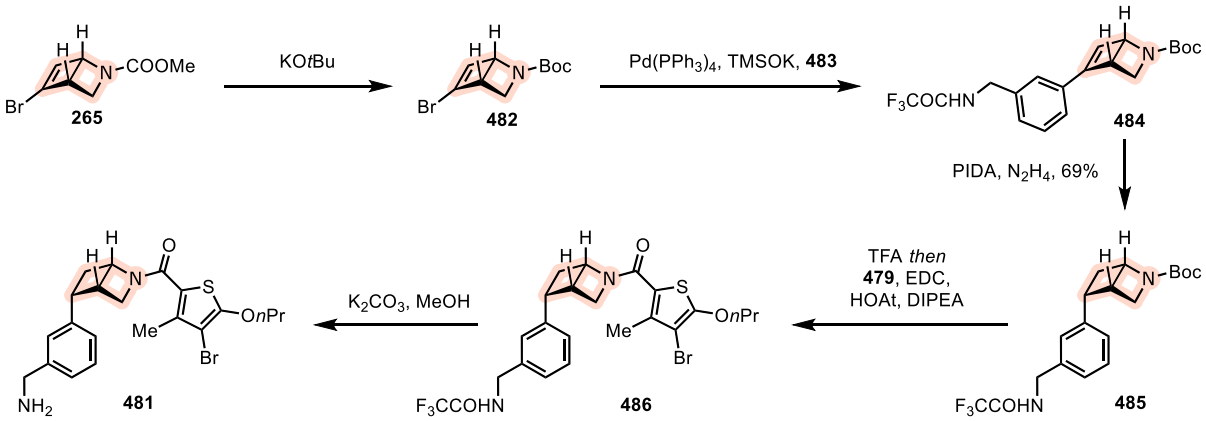
aqueous saturated NH_3) afforded a mixture of (5-(3-(aminomethyl)phenyl)-2-azabicyclo[2.2.0]hexan-2-yl)(4-bromo-3-methyl-5-propoxythiophen-2-yl)methanone (**476**) and (6-(3-(aminomethyl)phenyl)-2-azabicyclo[2.2.0]hexan-2-yl)(4-bromo-3-methyl-5-propoxythiophen-2-yl)methanone (**iso-476**) (135.7 mg, 0.30 mmol, 77% yield over 3 steps) as a slightly yellow viscous oil. *Constitutional isomer ratio of the products could not be determined with ^{1}H NMR due to signal overlap.*

MS (ESI-Q) calculated for $C_{21}H_{25}BrN_2O_2S+H^+$: 331, found: 331.

Synthesis of 2,2,2-trifluoro-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)acetamide (**483**)



Following the reported procedure, a 4 mL vial was charged with 2,2,2-trifluoro-*N*-(3-iodobenzyl)acetamide[147] (**477**, 131.6 mg, 0.400 mmol, 1.0 eq.), KOAc (96.4 mg, 0.982 mmol, 2-5 eq.), B_2Pin_2 (111.6 mg, 0.440 mmol, 1.1 eq.), $PdCl_2$(dppf) (13.6 mg, 0.019 mmol, 5 mol%) and anhydrous DMSO (2.4 mL, 0.17 M). The resulting mixture was heated to 80 °C overnight, cooled to room temperature and partitioned between Et_2O (50 mL) and water (50 mL). The organic phase was separated, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by RPLC (gradient elution, H_2O : MeCN = 65 : 35 ⟶ 0 : 100) to give 2,2,2-trifluoro-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)acetamide (**483**, 116.8 mg, 0.355 mmol, 89%) as a colorless clear oil. Its spectral data matches previously reported values.[149]



A 4 mL vial was charged with methyl 5-bromo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**265**, 87.2 mg, 0.40 mmol, 1.0 eq.) and THF (1.6 mL, 0.2 M). The resulting solution was cooled to 0 °C in an ice bath. KO*t*Bu solution (480 µL, 1M in THF, 0.48 mmol, 1.2 eq.) was canulated to the substrate solution. After the addition was complete, the ice bath was removed, and the resulting brown solution was stirred at room temperature overnight. The reaction solvent was removed under reduced pressure and the residue was loaded onto a column. Gradient elution with hexanes : Et_2O = 100 : 10 ⟶ 100 : 40 afforded *tert*-butyl 5-bromo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**482**, 72.4 mg, 0.28 mmol, 70%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 6.75 – 6.45 (m, 1H), 4.81 (m, 1H), 3.85 (m, 1H), 3.60 – 3.43 (m, 2H), 1.44 (s, 9H).

A 4 mL vial was charged with *tert*-butyl 5-bromo-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**482**, 72.4 mg, 0.28 mmol, 1.0 eq.), 2,2,2-trifluoro-*N*-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)acetamide (**483**, 117.1 mg, 0.36 mmol, 1.3 eq.) and $Pd(PPh_3)_4$ (16.7 mg, 0.01 mmol, 5 mol%) under nitrogen atmosphere. Anhydrous THF (0.9 mL, 0.2 M) was added, and the resulting solution was warmed up to 45 °C in a heating block. TMSOK (250 μL, 1 M solution in THF, 1.0 eq.) was added and the resulting mixture was stirred for 1.5 h. Afterwards, a second portion of TMSOK (140 μL, 1 M solution in THF, 0.5 eq.; 1.5 eq. in total) was added and the resulting mixture was stirred for an additional 1.5 h at the same temperature. The reaction mixture was cooled to room temperature, solvent was removed under reduced pressure, and the residue was purified via flash column chromatography. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 80 afforded *tert*-butyl 5-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**484**, 84.9 mg, 0.22 mmol, 80%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.41 – 7.24 (m, 4H), 6.84 (bs, 1H), 6.71 (m, 1H), 4.78 (m, 1H), 4.53 (m, 2H), 4.00 (bs, 1H), 3.65 (m, 1H), 3.48 (m, 1H), 1.43 (m, 9H).

Following the reported procedure[144], a 4 mL vial was charged with *tert*-butyl 5-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hex-5-ene-2-carboxylate (**484**, 84.9 mg, 0.22 mmol, 1.0 eq.), DCM (0.4 mL) and hydrazine hydrate (80 μL, 1.029 g/mL, 12.0 eq.). PIDA (193.2 mg, 0.60 mmol, 2.7 eq. in 2 mL DCM) was added dropwise over 3 hours using a syringe pump. Afterwards, the reaction mixture was left stirring overnight, quenched with saturated aqueous $NaHCO_3$ and extracted in DCM (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 40 ⟶ 100 : 80 afforded *tert*-butyl 5-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**485**, 59.0 mg, 0.15 mmol, 69%) as a colorless clear oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.36 (m, 1H), 7.20 – 7.04 (m, 3H), 6.80 (m, 1H), 4.64 – 4.37 (m, 3H), 4.01 (m, 2H), 3.71 (m, 1H), 3.29 (bs, *J* = 6.9 Hz, 1H), 2.91 (m, 1H), 2.76 – 2.52 (m, 1H), 1.43 (m, 9H).

A 4 mL vial was charged with *tert*-butyl 5-(3-((2,2,2-trifluoroacetamido)methyl)phenyl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**485**, 59.0 mg, 0.15 mmol, 1.0 eq.), DCM (0.6 mL) and TFA (0.15 mL, 1.490 g/mL, 2.0 mmol, 13 eq.). The resulting mixture was stirred for 15 minutes at room temperature. Solvent was removed under reduced pressure. Crude residue was redissolved in DMF (1.5 mL), and the resulting solution was cooled to 0 °C in an ice bath. Acid **479** (44.2 mg, 0.16 mmol, 1.0 eq.), HOAt (26.2 mg, 0.19 mmol, 1.3 eq.), DIPEA (100 μL, 0.742 g/mL, 0.57 mmol, 3.7 eq.) and EDC (36.8 mg, 0.19 mmol, 1.3 eq.) were added sequentially in one portion. The cooling bath was removed, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with EtOAc (50 mL), washed with 1 M aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$. Solvent was removed to yield crude amide **486** which was used in the next step without further purification.

MS (ESI-Q) calculated for $C_{23}H_{24}BrF_3N_2O_3S+H^+$: 545, found: 545.

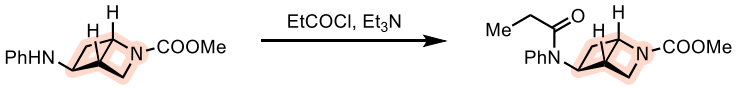
A 4 mL vial was charged with crude amide **486,** MeOH (1250 μL) and water (250 μL). K_2CO_3 (103.7 mg) was added to the resulting mixture in one portion. After stirring for 9 h at room temperature, solvent

was removed under reduced pressure and the residue was directly loaded onto a column. Gradient elution with DCM : MeOH = 100 : 5 ⟶ 100 : 20 (+ 1% aqueous saturated NH_3) afforded (5-(3-(aminomethyl)phenyl)-2-azabicyclo[2.2.0]hexan-2-yl)(4-bromo-3-methyl-5-propoxythiophen-2-yl)methanone (**481**, 49.7 mg, 0.11 mmol, 72% yield over 3 steps) as a slightly yellow viscous oil.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 7.32 (m, 1H), 7.21 (m, 1H), 7.15 (s, 1H), 7.08 (m, 1H), 4.91 (bs, 1H), 4.27 (bs, 1H), 4.07 (bs, 4H), 3.90 (s, 2H), 3.47 – 3.35 (m, 1H), 3.05 (m, 1H), 2.89 – 2.74 (bs, 1H), 2.65 (s, 2H), 2.44 (s, 3H), 1.85 (m, 2H), 1.06 (bs, 3H).

MS (ESI-Q) calculated for $C_{21}H_{25}BrN_2O_2S+H^+$: 331, found: 331.

Synthesis of fentanyl fragment isosteres **490** and **491**



337 **490**

A 4 mL vial was charged with methyl 5-(phenylamino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**337**, 24.0 mg, 0.10 mmol, 1.0 eq.) and DCM (1.0 mL, 0.1 M). The resulting solution was cooled to 0 °C in an ice bath. Et_3N (30 μL, 0.726 g/mL, 0.22 mmol, 2.1 eq.) and propionyl chloride (18 μL, 1.059 g/mL, 0.21 mmol, 2.0 eq.) were added sequentially in one portion. The resulting mixture was left stirring for 1 h at the same temperature, quenched with saturated aqueous $NaHCO_3$ and extracted with DCM (3 x 20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure, and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 100 ⟶ pure EtOAc afforded methyl 5-(*N*-phenylpropionamido)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**490**, 21.0 mg, 0.07 mmol, 71%) as a colorless clear oil.

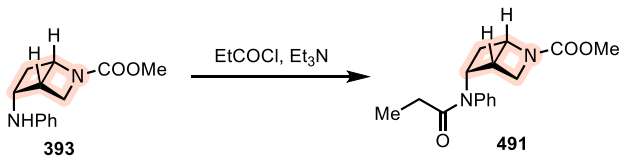
^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 7.43 (m, 2H), 7.39 (m, 1H), 7.09 (m, 2H), 5.04 (m, 1H), 4.37 (t, *J* = 8.8 Hz, 1H), 4.25 (bs, 1H), 4.07 (m, 1H), 3.64 (m, 3H), 2.94 (bs, 1H), 2.71 – 2.55 (m, 1H), 2.39 – 2.22 (m, 1H), 2.00 (m, 2H), 1.00 (m, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 174.1, 156.5, 140.5, 140.2, 129.9, 129.5, 128.5, 60.0, 59.4, 58.5, 58.2, 56.6, 55.6, 52.2, 39.4, 39.3, 35.7, 35.0, 28.7, 9.4.

R_f = 0.43 (hexanes : EtOAc = 1 : 2; UV)

IR (ATR-FTIR, cm^{-1}): 2954 (w), 2881 (w), 1705 (s), 1658 (m), 1484 (w), 1451 (m), 1384 (s), 1266 (w), 1122 (w), 768 (w), 705 (w).

HRMS (ESI-TOF) calculated for $C_{16}H_{20}N_2O_3+H^+$: 289.1552, found: 289.1547.



393 **491**

A 4 mL vial was charged with methyl 5-(phenylamino)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**393**, 63.4 mg, 0.27 mmol, 1.0 eq.) and DCM (2.7 mL, 0.1 M). The resulting solution was cooled to 0 °C in an ice bath. Et_3N (150 μL, 0.726 g/mL, 1.1 mmol, 4.0 eq.) and propionyl chloride (100 μL, 1.059 g/mL, 1.1

mmol, 4.0 eq.) were added sequentially in one portion. The cooling bath was removed, and the resulting mixture was left stirring for 1 h at room temperature. Afterwards, it was quenched with saturated aqueous $NaHCO_3$ and extracted with DCM (4 x 20 mL). Combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure, and loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 100 ⟶ 100 : 300 afforded methyl 5-(*N*-phenylpropionamido)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**491**, 68.9 mg, 0.24 mmol, 88%) as a clear colorless oil that solidifies on standing.

^{1}H NMR (600 MHz, $CDCl_3$, rotamers) δ 7.40 (m, 2H), 7.34 (m, 1H), 7.21 – 7.05 (m, 2H), 4.78 – 4.70 (m, 1H), 4.33 (m, 1H), 4.22 – 4.09 (m, 2H), 3.60 (m, 3H), 3.52 – 3.46 (bs, 1H), 2.52 – 2.44 (m, 1H), 2.13 (m, 1H), 1.98 (m, 1H), 1.86 (m, 1H), 0.99 (m, 3H).

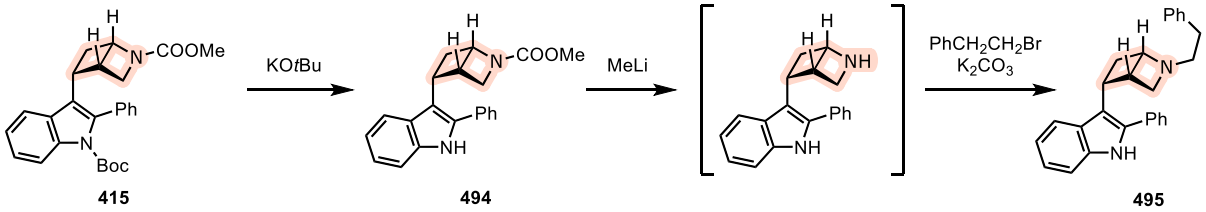
^{13}C NMR (151 MHz, $CDCl_3$, rotamers) δ 174.5, 156.3, 155.9, 140.2, 129.8, 129.3, 128.3, 128.3, 58.3, 57.7, 52.5, 52.3, 52.2, 51.0, 50.2, 36.4, 33.1, 32.6, 28.3, 9.4.

R_f = 0.40 (hexanes : EtOAc = 1 : 2; UV)

IR (ATR-FTIR, cm^{-1}): 2953 (w), 1703 (s), 1655 (s), 1484 (w), 1493 (m), 1379 (s), 1263 (w), 1125 (m), 768 (w), 703 (w).

HRMS (ESI-TOF) calculated for $C_{16}H_{20}N_2O_3$+H^+: 289.1552, found: 289.1548.

Synthesis of h5-HT_{2A} antagonist isostere **495**



A 4 mL vial was charged with *tert*-butyl 3-(2-(methoxycarbonyl)-2-azabicyclo[2.2.0]hexan-5-yl)-2-phenyl-1H-indole-1-carboxylate (**415**, 12.5 mg, 0.03 mmol, 1.0 eq.) and anhydrous THF (150 μL) under nitrogen atmosphere. The resulting solution was cooled to 0 °C in an ice bath. KO*t*Bu solution (60 μL, 0.6M in THF, 0.03 mmol, 1.2 eq.) was canulated to the substrate solution. After the addition was complete, the ice bath was removed, and the resulting brown solution was stirred at room temperature for 5 h. The reaction solvent was removed under reduced pressure and the residue loaded onto a column. Gradient elution with hexanes : EtOAc = 100 : 20 ⟶ 100 : 60 afforded methyl (5-(2-phenyl-1H-indol-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**494**, 7.1, 0.02 mmol, 74%) as a colorless film.

^{1}H NMR (500 MHz, $CDCl_3$, rotamers) δ 8.14 (s, 1H), 7.55 (m, 1H), 7.43 – 7.34 (m, 6H), 7.20 (m, 1H), 7.11 (m, 1H), 4.64 – 4.48 (m, 1H), 4.37 (m, 1H), 4.04 – 3.93 (m, 1H), 3.78 (m, 1H), 3.57 (s, 3H), 3.42 (m, 1H), 3.06 (m, 1H), 2.65 (m, 1H).

MS (ESI-Q) calculated for $C_{21}H_{20}N_2O_2$+H^+: 333, found: 333.

A 4 mL vial was charged with metyl (5-(2-phenyl-1H-indol-3-yl)-2-azabicyclo[2.2.0]hexane-2-carboxylate (**494**, 7.1 mg, 0.02 mmol, 1.0 eq.) and anhydrous THF (0.2 mL, 0.1 M) under nitrogen atmosphere. The resulting solution was cooled to -10 °C and MeLi solution (100 μL, 1.6 M in Et_2O, 7.5

eq.) was slowly added. The resulting mixture was warmed up to -5 °C and left stirring for 20 minutes. Afterwards, it was quenched with water and extracted with EtOAc (50 mL). The organic phase was separated, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield crude amine, which was taken forward without further purification.

MS (ESI-Q) calculated for $C_{19}H_{18}N_2+H^+$: 275, found: 275.

A 4 mL vial was charged with the crude amine from the step above, DMF (0.2 mL), K_2CO_3 (5.5 mg, 0.04 mmol, 1.9 eq.) and (2-bromoethyl)benzene (6 μL, 1.360 g/mL, 0.04 mmol, 2.0 eq.). The resulting suspension was stirred at room temperature overnight. The reaction solvent was removed under high vacuum and the residue directly loaded onto a column. Gradient elution with DCM : MeOH = 100 : 2 ⟶ 100 : 8 afforded 3-(2-phenethyl-2-azabicyclo[2.2.0]hexan-5-yl)-2-phenyl-1H-indole (**495**, 3.8 mg, 0.01 mmol, 47% yield over two steps) as a colorless film.

MS (ESI-Q) calculated for $C_{27}H_{26}N_2+H^+$: 379, found: 379.

Crystallographic data

Single crystals of $C_{16}H_{17}FeNO$ (**363**, CCDC 2257526) were crystallized by vapor diffusion of hexanes into a solution of **363** in ethyl acetate. A suitable crystal was selected and mounted using Paratone-N oil (Exxon) on a Cryo-Loop (Hampton research) with (1 5 1) face roughly perpendicular to the spindle axis on a Bruker APEX-II CCD diffractometer. The crystal was kept at 100.00 K during data collection. Using Olex2[150], the structure was solved with the XT[151] structure solution program using Intrinsic Phasing and refined with the XL[152] refinement package using Least Squares minimization.

Identification code	CCDC 2257526
Empirical formula	$C_{16}H_{17}FeNO$
Formula weight	295.15
Temperature/K	100.00
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	9.8978(3)
b/Å	13.1247(3)
c/Å	9.7456(3)
α/°	90
β/°	91.3690(10)
γ/°	90
Volume/Å^3	1265.65(6)
Z	4
ρ_{calc}g/cm^3	1.549

μ/mm^{-1}	1.181
F(000)	616.0
Crystal size/mm^3	0.273 × 0.159 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.156 to 56.656
Index ranges	-13 ≤ h ≤ 13, -17 ≤ k ≤ 17, -13 ≤ l ≤ 13
Reflections collected	35537
Independent reflections	3151 [R_{int} = 0.0420, R_{sigma} = 0.0174]
Data/restraints/parameters	3151/0/172
Goodness-of-fit on F^2	1.042
Final R indexes [I>=2σ (I)]	R_1 = 0.0233, wR_2 = 0.0577
Final R indexes [all data]	R_1 = 0.0261, wR_2 = 0.0597
Largest diff. peak/hole / e $Å^{-3}$	0.40/-0.27

Single crystals of $C_{16}H_{20}N_2O_3$ (**491**, CCDC 2257525) were crystallized by vapor diffusion of hexanes into the ethyl acetate solution of **491**. A suitable crystal was selected and mounted using Paratone-N oil (Exxon) on a Cryo-Loop (Hampton research) with (-1 3 5) face roughly perpendicular to the spindle axis on a Bruker APEX-II CCD diffractometer. The crystal was kept at 100.00 K during data collection. Using Olex2 [1], the structure was solved with the XT [2] structure solution program using Intrinsic Phasing and refined with the XL [3] refinement package using Least Squares minimisation.

Identification code	CCDC 2257525
Empirical formula	C16H20N2O3
Formula weight	288.34
Temperature/K	100
Crystal system	triclinic
Space group	P-1
a/Å	7.6371(2)
b/Å	8.8000(2)
c/Å	11.9968(3)
α/°	93.2950(10)
β/°	101.9880(10)
γ/°	107.4030(10)
Volume/Å3	746.37(3)
Z	2

ρcalcg/cm3	1.283
μ/mm-1	0.089
F(000)	308
Crystal size/mm3	0.408 × 0.353 × 0.351
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.638 to 56.69
Index ranges	-10 ≤ h ≤ 10, -11 ≤ k ≤ 11, -16 ≤ l ≤ 16
Reflections collected	52260
Independent reflections	3708 [Rint = 0.0242, Rsigma = 0.0139]
Data/restraints/parameters	3708/0/192
Goodness-of-fit on F2	1.03
Final R indexes [I>=2σ (I)]	R1 = 0.0365, wR2 = 0.0958
Final R indexes [all data]	R1 = 0.0376, wR2 = 0.0967
Largest diff. peak/hole / e Å-3	0.30/-0.19

11. ACKNOWLEDGEMENT OF CONTRIBUTIONS

Alexander S. Shved performed computational studies (*i.e.* conformational analysis and thermochemistry calculations) and single crystal X-ray analysis. Dr. Yaroslav D. Boyko and Jan Petrovčič explored the reactivity of 2-azabicyclo[2.2.0]hex-5-enes and their "hydrofunctionalized" derivatives. Separation of constitutional isomers was performed by Merck separation team. The rest of synthetic work, reaction optimization, isostere synthesis, characterization, structure elucidation and computational data analysis was done by Jan Petrovčič. Giovanni Lenardon's help is acknowledged for providing experimental set-up pictures, reaction scale-ups, workups, purifications and characterizations.

12. REFERENCES

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